

Low- versus standard-dose alteplase in patients on prior antiplatelet therapy: the ENCHANTED trial

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Abstract

Background and Purpose: Many patients receiving thrombolysis for acute ischemic stroke (AIS) are on prior antiplatelet therapy (APT), which may increase symptomatic intracerebral hemorrhage (sICH) risk. In a pre-specified subgroup analysis, we report comparative effects of different doses of intravenous (iv) alteplase according to prior APT use among participants of the international multi-center ENhanced Control of Hypertension And Thrombolysis stroke stuDy.

Methods: Among 3285 alteplase-treated patients (mean age 66.6 years, 38% female) randomly assigned to low-dose (0.6mg/kg) or standard-dose (0.9mg/kg) iv alteplase within 4.5 hours of symptom onset, 752 (22.9%) reported prior APT use. Primary outcome at 90-days was the combined endpoint of death or disability (modified Rankin scale [mRS] scores 2-6). Other outcomes included mRS scores 3-6, ordinal mRS shift, and sICH by various standard criteria.

Results: There were no significant differences in outcome between patients with and without prior APT after adjustment for baseline characteristics and management factors over the first week; defined by mRS scores 2-6 (adjusted odds ratio 1.01, 95% confidence interval [CI] 0.81-1.26; p=0.953), 3-6 (0.95 [0.75-1.20]; p=0.662) or ordinal mRS shift (1.03 [0.87-1.21]; p=0.770). Alteplase-treated patients on prior APT had higher sICH (1.82 [1.00-3.30]; p=0.051) according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition. Although not significant (p trend 0.053), low-dose alteplase tended to have better outcomes than standard-dose in those on prior APT compared to those not using APT (mRS scores of 2-6, 0.84 [0.62-1.12] vs. 1.16 [0.99-1.36]).

Conclusions: Low-dose alteplase may improve outcomes in thrombolysis-treated AIS patients on prior APT, but this requires further evaluation in a randomized controlled trial.

Clinical Trial Registration: Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>.

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Intravenous alteplase (recombinant tissue plasminogen activator [rt-PA]) is the only approved medical reperfusion treatment in patients with acute ischemic stroke (AIS); and the earlier the treatment is given, the greater the proportional benefit.¹ As up to 40% of AIS patients have regularly taken antiplatelet therapy (APT), mainly aspirin, at the time of intravenous alteplase,²⁻⁴ a harmful interaction between these two agents may reduce the net benefit of thrombolysis treatment. Two recent meta-analyses of randomized controlled trials and cohort studies have both reported that APT use at the time of alteplase significantly increases the risk of symptomatic intracerebral hemorrhage (sICH).^{5,6} Pan and colleagues reported that this was associated with a reduced probability of good outcome (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.73 to 1.01; $p=0.06$),⁶ though others have not reported any clear attenuation of the clinical benefit.⁷ However, the Antiplatelet therapy in combination with rt-PA in Thrombolysis in Ischemic Stroke (ARTIS) trial, the only randomized trial of de novo aspirin with standard-dose alteplase versus standard-dose alteplase alone, was terminated prematurely because of an excess sICH in the combination arm (absolute difference 2.8%, 95%CI 0.2 to 5.4%; $p=0.04$).⁸

Concerns over the risk of sICH with intravenous alteplase has led to lower doses being used in many AIS patient groups, particularly Asians,⁹ 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 (0.6mg/kg body weight) compared to a standard-dose (0.9mg/kg) of intravenous alteplase in patients with AIS who fulfil guideline-recommended criteria for thrombolysis treatment.¹⁰ Whilst the ENCHANTED trial failed to meet its primary non-inferiority outcome, a pre-specified subgroup analysis identified a borderline significant interaction ($p=0.052$) between prior APT use and alteplase dose on the primary outcome, the conventional binary separation of scores of 2-6 that define death or disability on the modified Rankin scale (mRS).¹⁰ We report herein,

more details of the balance of benefits and risks of alteplase according to prior APT use, and potential modification of effects by use of low-dose alteplase.

Materials and Methods

Patients

The ENCHANTED trial is an international, multi-center, prospective, randomized, open-label, blinded-endpoint trial which used a 2x2 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 (BP) in the ongoing arm; full details of which are outlined elsewhere.¹⁰ This analysis considers the alteplase dose arm, where 3310 patients with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for thrombolysis treatment administered within 4.5 hours of symptom onset, were randomly assigned to receive low-dose (0.6mg/kg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose (0.9mg/kg; 10% as bolus, 90% as infusion over 1 hour) intravenous alteplase. The study protocol was approved by the appropriate ethics committee at each participating center, and written informed consent was obtained from the patient or an appropriate surrogate.

Procedures

Key demographic and clinical characteristics, including the prior use of aspirin and/or another APT agent were recorded at the time of enrollment. Stroke severity was measured using the National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, 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 DICOM format on a CD-ROM identified only with the patient's unique study number, and analyzed centrally for any intracranial hemorrhage by independent assessors blinded to clinical data, treatment, and date

and sequence of scan. Assessors graded any identified hemorrhage as intracerebral using a range of standard definitions (see Supplemental Materials) 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 to 6 on the mRS. Other efficacy outcomes included an ordinal mRS shift, and the combined endpoint of death or major disability (mRS scores of 3 to 6) at 90 days. The secondary (safety) outcome was sICH, defined according to several criteria from other studies (see Supplemental Materials).

Statistical analysis

The association of prior APT on global functional outcome was estimated using ordinal logistic regression after the assumption of proportionality of the odds was confirmed from a likelihood ratio test. Logistic regression models were used to estimate associations for all the other outcomes. Adjustments were made for the pre-specified minimization and baseline covariates, and additionally for aspects of management over the first seven days following hospital admission. In patients with and without prior APT, the heterogeneity of alteplase treatment effects was tested by adding interaction terms to the statistical models. Two-sided P values are reported and $P < 0.05$ was considered statistically significant. The SAS version 9.3 (SAS Institute, Cary, NC) 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 final responsibility for the decision to submit the paper for publication.

Results

Baseline Characteristics

These analyses included 3285 patients (38% female; mean age 66.6 years), in whom the presence or absence of prior APT use was recorded (Supplemental Figure I); 752 (22.9%) patients reporting the use of prior APT at baseline. Those with prior APT were older, and more likely to be of non-Asian ethnicity, had baseline imaging changes indicative of more severe cerebral infarction, and were diagnosed with a presumed cardioembolic or ‘other’ stroke pathology (Supplemental Table I). Patients on prior APT were also more likely to have associated co-morbidity (including hypertension, previous stroke, coronary artery or other cardiac disease or risk factor including atrial fibrillation, diabetes mellitus, and hypercholesterolemia), and to be on statin therapy (Supplemental Table I). However, with the exception of a history of hypercholesterolemia and use of statins, there were no baseline imbalances between the use of low-dose or standard-dose alteplase in patients on prior APT (Table 1). Overall, patients with prior APT were treated more quickly after the onset of symptoms and received a higher bolus alteplase dose, but there were no other significant differences in thrombolysis-associated management (Supplemental Table II).

Prior APT and outcome

Prior APT was associated with a worse 90-day clinical outcome, whether defined by mRS scores of 2 to 6 (unadjusted OR 1.38, 95%CI 1.17-1.63; $p<0.001$), 3 to 6 (1.33, 1.13-1.58; $p<0.001$), or ordinal shift (1.41, 1.22-1.63; $p<0.001$), or mortality alone (1.46, 1.12 to 1.89; $p=0.005$) (Supplemental Table III). However, after adjustment for the minimization criteria and important baseline variables at the time of randomization, and subsequently for imbalances in management during the first seven days of hospital admission, there were no significant differences in these outcomes between patients with and without prior APT (Supplemental Table III). Prior APT was also associated with an increased risk of sICH across most definitions (Supplemental Table IV).

Prior APT and alteplase dose

Although not significant, low-dose alteplase tended to have more favorable 90-day outcomes in patients on prior APT compared to those without prior APT, defined by mRS scores of 2-6 (unadjusted OR 0.84 [0.62-1.12] vs. 1.16 [0.99-1.36], respectively; p trend 0.053), 3-6 (OR 0.80 [0.60-1.08] vs. 1.10 [0.93-1.30]; p trend 0.065) (Supplemental Table V), or as an ordinal mRS shift analysis (0.76 [0.59-0.88] vs. 1.07 [0.93-1.23]; p interaction 0.023) (Figure 1). Conversely, for those patients without prior APT, 77% of the ENCHANTED population, standard-dose alteplase was associated in a trend towards more favorable outcome (Supplemental Table V). Importantly, tThere was reduced mortality by 5.0% (-0.05 to 9.95) and 1.1% (-1.13 to 3.40) in patients with and without prior APT (p interaction 0.23) treated with low-dose compared to standard-dose alteplase, but no significant differences in sICH across a broad range of definitions (Figure 2, Supplemental Table VI).

Discussion

These additional analyses of the ENCHANTED trial related to the patient subgroup on prior APT have shown that, albeit not significant, a trend towards more favorable clinical outcomes with low-dose as compared to standard-dose intravenous alteplase, warranting further evaluation in a randomized controlled trial. Patients on prior APT account for at least one quarter of the thrombolysis-eligible AIS population, as indicated by an international stroke thrombolysis registry,² the United States Get With the Guidelines (GWTG) quality improvement registry,⁴ and participants in the ENCHANTED trial, and who are at significantly higher risk of sICH³ and poor outcome¹¹ compared to other patients who receive alteplase. This figure may increase further with the aging of population and data suggesting benefits of early use of aspirin in reducing the risk of secondary ischemic events after transient ischemic attack or minor ischemic stroke.¹²

Our findings are consistent with previous studies of patients on prior APT being at greater risk of thrombolysis-associated sICH, in part related to the greater co-occurrence of other risk

variables such as older age, statin use, cardiac disease, atrial fibrillation, and diabetes mellitus.^{4,5} Whilst higher sICH with APT may explain much of the association with worse functional outcome after AIS, the presence of greater co-morbidity is also likely to be particularly relevant.¹³ The GWTG registry showed that aspirin monotherapy was associated with increased sICH after adjustment for baseline imbalances (aOR 1.18, 95%CI 1.10-1.28).⁴

The ENCHANTED trial allowed for a randomized assessment of the comparative effects of low-dose versus standard-dose alteplase in patients on prior APT. Concerns of a higher risk of sICH have led to a wide range of doses of intravenous alteplase being used in many Asian countries in relation to perceived risks and affordability of the treatment.⁹ Although three studies - two registries^{14,15} and one observational¹⁶ - have specifically evaluated outcomes by dose of alteplase in Asian populations, only Chao and colleagues reported a trends towards an adverse effect of prior APT on outcome.¹⁶ In particular, use of clopidogrel or ticlopidine, but not aspirin, was associated with an increased risk of sICH on multivariate analysis. However, only 3.4 and 4.0% of patients in the low- and standard-dose groups, respectively, were on these agents, and no beneficial effect of low-dose alteplase in patients on prior APT was observed.¹⁶ Nonetheless, as low-dose alteplase in the ENCHANTED trial was associated with lower sICH, this may be considered an important treatment option in such patients, despite the absence of any clear reduction in sICH in those patients on prior APT.

Some authors have suggested that prior APT may result in less severe strokes, by limiting the size of the occluding thrombus and subsequent risk of embolization,¹⁷ improving recanalization,¹⁸ or the microcirculation of the ischemic penumbra through inhibition of platelet-derived vasoconstrictors (e.g. thromboxane A₂),¹⁹ and of potential anti-inflammatory and neuroprotective effects.²⁰ Most recently, a retrospective analysis of a large multicenter registry of 10,433 patients indicated better outcomes in those on prior APT after atherothrombotic stroke, but not after cardioembolism or small vessel occlusion, and only in

patients without hemorrhagic transformation.²¹ However, Ricci and colleagues found no association of previous aspirin use with baseline stroke severity in the Third International Stroke Trial.²² Additionally, Pan and colleagues did not demonstrate increased recanalization rate in patients on prior APT in their meta-analysis.⁶ In ENCHANTED, more patients in the prior APT group had atrial fibrillation and a final diagnosis of cardioembolic stroke, features which may suggest a lower efficacy of low-dose alteplase due to proximal vessel occlusion and greater clot burden. Nonetheless, low-dose alteplase was associated with better clinical outcome on shift analysis of 90-day mRS.

On the basis of these current data, many study protocols and guidelines have recommended that APT be avoided for at least 24 hours after the use of alteplase.²³ Although higher sICH was seen with de novo use of aspirin at the time of thrombolysis in the ARTIS trial,⁸ only 3 (0.53%) episodes of sICH (according to the SITS-MOST definition) occurred among 571 patients who also received antithrombotic therapy (antiplatelet or heparin) within the first 24 hours after thrombolysis in the ENCHANTED trial. These numbers are too small to offer a reliable assessment of risk, or to assess differences according to variable doses of alteplase. However, the Cochrane review of thrombolysis trials concluded that the odds of mortality increases with early administration of APT; the majority of this risk occurring in the first 24 hours.²⁴

Another important aspect of APT in AIS relates to both the type, number and combination of prior agents, for which the data are scarce, but a significant dose-response in relation to the number of antiplatelet agents prescribed has been reported.^{5,6} A higher sICH risk was noted in thrombolysis-treated patients on combination therapy, in particular aspirin and clopidogrel, who were registered in the Virtual International Stroke Trials Archive database.²⁵ Such an association was also noted in the SITS International Stroke Thrombolysis Register³ and the GWTG registry cohort where the combination aspirin and clopidogrel was associated with a

number needed to harm of 60 compared to 147 for aspirin monotherapy.⁴ Nonetheless, low numbers of patients and sICH in all these studies limits the reliability of these data and the recommendations that can be made for clinical practice. Moreover, uncertainty exists over the role of newer antiplatelet agents in the setting of thrombolysis for AIS, although a small pilot phase trial demonstrated safety of a glycoprotein IIb/IIIa inhibitor with low-dose alteplase.²⁶ Being a pragmatic academic study, ENCHANTED is unable to provide any information about the relation of type, dose, combination, duration, indication and timing of the last dose of APT prior to thrombolysis to adverse outcomes, although it would seem reasonable to assume that aspirin monotherapy was the most commonly prescribed antiplatelet regimen used in participating countries.

Other limitations of our study include those related to an open-label trial, despite our efforts to minimize 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 trials¹ or registries,²⁷ there may be concerns over the generalizability of these data, while imprecision in the estimates of the treatment effect may have arisen from the timing and inter-observer variability in scoring of the mRS.²⁸

Conclusions

Our study suggests that the use of low-dose, as compared to standard-dose, intravenous alteplase may be associated with improved clinical outcome in patients who were on prior APT. ~~Therefore, wTaken together with the overall results of the ENCHANTED trial, clinicians who are concerned over the risk of sICH and adverse outcomes may wish to consider use of low-dose alteplase.~~ We consider a formal evaluation of low- versus standard-dose alteplase in a randomized controlled trial of patients on prior APT is warranted. In

addition, the potential beneficial effects of low-dose alteplase in other patient groups considered at high risk of sICH ~~cs~~ should be considered.²⁹

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Table 1: Baseline characteristics by randomized treatment among patients on prior antiplatelet therapy

	Randomized treatment group		P value
	Low-dose (n=407)	Standard-dose (n=345)	
Time from stroke onset to randomization (hrs), mean (SD)	2.6 (0.9)	2.7 (0.9)	0.084
Female, n (%)	160 (39.3)	136 (39.4)	0.976
Age (years), mean (SD)	71.0 (11.1)	71.9 (11.2)	0.310
≥80, n (%)	84 (20.6)	80 (23.2)	0.399
Ethnicity, Asian	186 (45.7)	138 (40.0)	0.116
Clinical features			
Systolic BP (mmHg), mean (SD)	148.4 (18.8)	149.9 (20.3)	0.309
Diastolic BP (mmHg), mean (SD)	82.4 (13.2)	82.3 (12.9)	0.857
Heart rate (beats per minute), mean (SD)	79.7 (18.1)	78.1 (15.6)	0.186
NIHSS score*			
Median (Q1, Q3)	8 (5-15)	8 (5-14)	0.836
≥14, n (%)	112 (27.5)	91 (26.4)	0.725
GCS score †, median (Q1, Q3)	15 (13-15)	15 (14-15)	0.568
Visible early ischemic changes on brain imaging, n (%)	124 (30.5)	90 (26.1)	0.185
Mass effect on brain imaging, n (%)	8 (2.0)	5 (1.5)	0.588
Medical history			
Hypertension, n (%)	321 (78.9)	263 (76.2)	0.367
Currently treated hypertension, n (%)	301 (74.0)	243 (70.4)	0.282
Previous stroke, n (%)	125 (30.7)	122 (35.4)	0.176
Coronary artery disease, n (%)	148 (36.4)	107 (31.0)	0.123
Valvular or other heart disease, n (%)	57 (14.0)	47 (13.6)	0.880

Atrial fibrillation confirmed on ECG, n (%)	128 (31.5)	92 (26.7)	0.151
Diabetes Mellitus, n (%)	107 (26.3)	89 (25.8)	0.878
Hypercholesterolemia, n (%)	165 (40.5)	112 (32.5)	0.022
Current smoker, n (%)	64 (15.8)	58 (16.9)	0.685
Pre-stroke function without any symptoms (mRS=0)	125 (30.7)	118 (34.2)	0.308
Warfarin anticoagulation, n (%)	10 (2.5)	3 (0.9)	0.096
Statin or other lipid lowering agent, n (%)	216 (53.2)	152 (44.0)	0.013
Final diagnosis at time of hospital separation			
Non-stroke, n (%)	16 (4.0)	10 (2.9)	0.442
Presumed stroke pathology, n (%)			
Large artery occlusion due to significant atheroma	115 (29.8)	112 (33.8)	0.323
Small vessel or perforating vessel lacunar disease	56 (14.5)	56 (16.9)	
Cardio-embolism	133 (34.5)	95 (28.7)	
Other or uncertain etiology	82 (21.2)	68 (20.5)	

Data are n (%), mean (SD), or median (Q1, Q3). The P values are based on Chi-square, T test, or Wilcoxon signed-rank test

NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow coma scale, mRS: modified Rankin scale,

CT: computerized tomography, MRI: magnetic resonance imaging

*Scores on the National Institutes of Health stroke scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficits.

†Scores on the Glasgow coma scale (GCS) range from 15 (normal) to 3 (deep coma)

Figure Legends

Figure 1: Global functional outcome at 90 days in patients with and without prior antiplatelet therapy by randomized treatment

Footnote: The figure shows the raw distribution of scores on the modified Rankin scale (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 odds ratios (and 95% confidence intervals) are provided for ordinal shift of mRS between low- and standard-dose intravenous alteplase by patients with and without prior use of antiplatelet therapy and acute ischemic stroke.

Figure 2: Symptomatic intracerebral hemorrhage in patients with and without prior antiplatelet use, by randomized treatment

Footnote: The figure shows the rates of symptomatic intracerebral hemorrhage (sICH) on follow-up neuroimaging for patients treated with low-dose and standard-dose intravenous alteplase for acute ischemic stroke, overall and for patients with and without prior antiplatelet therapy. Definitions of sICH shown include: Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), National Institute of Neurological Disorders and Stroke (NINDS), European Cooperative Acute Stroke Study 2 (ECASS2) and 3 (ECASS3), and fatal. The overall effect is represented by the open diamond for each sICH definition. For subcategories, black diamonds represent point estimates and horizontal lines represent 95% confidence intervals.