Who will benefit more from low-dose alteplase in acute ischemic stroke?

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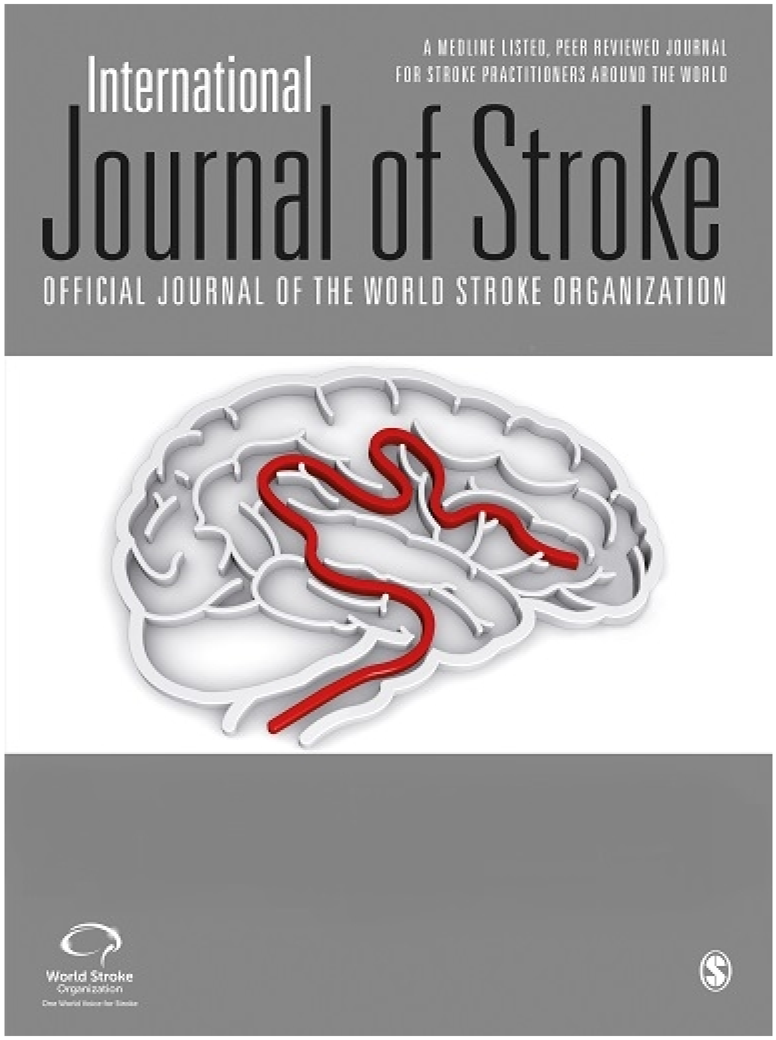

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Who will benefit more from low - dose alteplase in acute ischaemic stroke?

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Abstract

Objectives

Controversy persists over the benefits of low- versus standard-dose intravenous alteplase for treatment of acute ischaemic stroke (AIS). We sought to determine individual patient factors that contribute to the risk-benefit balance of low-dose alteplase treatment..

Methods

Observational study using data from the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), an international, randomised, open-label, blinded-endpoint trial that assessed low-dose (0·6mg/kg) versus standard-dose (0·9mg/kg) intravenous alteplase in AIS patients. Logistic regression models were used to estimate the benefit of good functional outcome (scores 0 or 1 on the modified Rankin scale [mRS] at 90-days) and risk (symptomatic intracerebral haemorrhage [sICH]), under both regimens for individual patients. The net advantage for low-dose, relative to standard-dose, alteplase was calculated by dividing excess benefit by excess risk according to a combination of patient characteristics. The algorithms were externally validated in a nationwide acute stroke registry database in South Korea.

Results

Patients with an estimated net advantage from low-dose alteplase, compared with without, were younger (mean age of 66 vs. 75 years), had lower systolic blood pressure (BP) (148 vs. 160 mmHg), lower National Institute of Health Stroke Scale score (median of 8 vs. 16), and no atrial fibrillation (AF) (10.3% vs. 97.4%), diabetes mellitus (DM) (19.2% vs. 22.4%) or pre-morbid symptoms (defined by mRS=1) (16.3% vs. 37.8%).

Conclusion

Use of low-dose alteplase may be preferable in AIS patients with a combination of favourable characteristics, including younger age, lower systolic BP, mild neurological impairment, and no AF, DM, or pre-morbid symptoms.

INTRODUCTION

Alteplase is the only established thrombolytic treatment for acute ischaemic stroke (AIS), with most guidelines recommending an intravenous dose of 0·9 mg/kg for eligible AIS patients.(1, 2) However, the are data to suggest that Asians are at increased risk for symptomatic intracerebral haemorrhage (sICH); this led to a lower dose of 0·6 mg/kg of alteplase being approved in Japan,(3, 4) which has been variably adopted by clinicians elsewhere in Asia and beyond.

In the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED),[5-7] low-dose alteplase was not found to be statistically non-inferior to a standard-dose alteplase on the conventional binary outcome of death or any disability, defined by scores 2 to 6 on the modified Rankin scale (mRS) at 90 days after the onset of symptoms.[7] However, low-dose alteplase was found to be non-inferior for overall functional recovery, through ordinal analysis of the mRS, and to clearly reduce the risk of sICH, the most worrisome complication of this treatment.(5-7)

A combination of patient characteristics may influence the risk-benefit balance of low-dose relative to standard-dose alteplase in AIS patients.(8-10) The aim of this study was to develop clinical prediction models that incorporate plausible risk and benefit estimates in order to determine individual patient factors that contribute to the risk-benefit balance of low-dose compared with standard-dose alteplase treatment.

METHODS

Development cohort

The ongoing ENCHANTED trial is an international, multi-centre, quasi-factorial, prospective, randomised, open-label, blinded-endpoint trial; the details of which are outlined elsewhere.(5-7) The alteplase-dose arm of the trial has concluded, where 3310 patients with a clinical diagnosis of

AIS confirmed on brain imaging and fulfilling standard criteria for thrombolysis treatment, including symptom onset within 4.5 hours, were randomly assigned to receive low- (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) alteplase. The intensity of blood pressure (BP) control arm of the trial is ongoing and due to report results in 2019. The study protocol was approved by the appropriate ethics committee at each participating centre, and written informed consent was obtained from each patient or an appropriate surrogate.

Key demographic and clinical characteristics were recorded at the time of enrolment of patients, with the severity of neurological impairment measured using the National Institutes of Health Stroke Scale (NIHSS) at baseline, 24 hours, and at Day 7 (or on discharge from hospital where this was earlier). Digital images of all baseline and follow-up CT, MRI and angiogram images, were uploaded for central review by independent assessors blind to clinical data, treatment, and date and sequence of scan using MIStar version 3·2 (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia). Assessors graded any haemorrhage as intracerebral, subarachnoid, intraventricular, subdural or other; sICH was graded across all standard definitions.(7)

Validation cohort

Study subjects were selected from a prospective, multi-centre, nationwide acute stroke registry database in South Korea, which was established in April 2008 and described in detail elsewhere.(11, 12) The collaborative registry study group consisted of 15 academic and regional stroke centres as of July 2014. Participating centres enrolled consecutive acute stroke cases admitted within 7 days from onset into a web-based database system. Study data were regularly audited by the central adjudication committee using pre-specified query sequences. Acute stroke management, including use of recanalization therapy, was performed according to current clinical guidelines and institutional protocols, at the discretion of individual physicians who managed the patients.(13) Information on patient characteristics and treatments were obtained from the registry database.

Outcomes

A beneficial outcome was defined as excellent functional recovery according to scores 0 or 1 on the mRS at 90 days: this was the primary efficacy outcome in the alteplase-dose arm of the ENCHANTED trial. A risk outcome was defined as sICH according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).

Statistical analysis

Two logistic regression models were developed: one for the prediction of benefit and the other for the prediction of risk. Significant predictors ($P<0.1$) from the univariate analyses and randomised dose arm were tested for their associations with outcomes in multivariable models. The full models were reduced by successively removing the non-significant covariates until all the remaining predictors remained statistically significant ($P<0.05$). Randomised treatment group was forced into the models. Collinearity and interaction between variables were checked. Significant two-way and three-way interactions ($P <0{\cdot}05$) between variables were included in models. The models were validated in the South Korean acute stroke registry database. Performance of the final prediction models was assessed using an area under the receiver-operating-characteristic curve (AUROC), with c-statistic for discriminative ability and the Hosmer–Lemeshow goodness-of-fit statistic for calibration.(14)

The models were constructed to estimate the probabilities of benefit and risk for any patient according to low- and standard-dose alteplase. The treatment variable was fixed in turn to low-dose and standard-dose alteplase, with the probabilities of benefit and risk for subject *i* represented as B_i^L and B_i^S, and R_i^L and R_i^S, respectively, for the two doses. The net advantage of low-dose alteplase is defined as $(B_i^L - B_i^S)$ / $(R_i^L - R_i^S)$. A net advantage >1 therefore indicates the superiority of low-dose alteplase. However, this methodology assumes that benefit and risk have equal weight, which may not be acceptable to some clinicians. Thus, a weighted net advantage was assigned as $w(B_i^L - B_i^S)\ /\ (1 - w)(R_i^L - R_i^S)$, where w is the relative weight (between 0 and 1) given to benefit. For example, if the risk of harm from sICH is considered to be more important, and the clinician should wish to disregard potential functional benefits from treatment, *w* should be set close to 0. Conversely, if the risk of harm from sICH is considered to be less important, and wishes to focus on positive functional outcome, then *w* should be set close to 1. The equations to estimate the probabilities were shown in SFigure I. Two-sided P values were reported and P <0·05 was considered statistically significant. SAS version 9·3 (SAS Institute, Cary, NC) was used in all analyses.(5)

Results

Model development and performance

All patients with complete information (n=3197) were included in the benefit analysis: 1530 patients (47·8%) had an excellent outcome; 48·9% and 46.8% had an excellent outcome in the low-dose and standard-dose alteplase groups, respectively. The characteristics of included patients by mRS scores 0-1 versus 2-6 are shown in STable 1. Patients with an excellent functional outcome were significantly more likely to be young, male, of Asian ethnicity, with a mild neurological deficit, with fewer co-morbidities (including previous stroke, coronary artery disease, diabetes mellitus [DM], and atrial fibrillation [AF]), and lower prior use of warfarin, aspirin, and statin therapy, at baseline. After successively removing non-significant covariates from the multivariable model, only age, systolic BP, baseline NIHSS score, pre-morbid level of function [estimated mRS score], and history of AF and DM remained significant. Randomized treatment group was forced into the model to estimate the predicted probabilities according to alteplase dose. A significant interaction between age and AF was identified and included in the model (Table 1). No collinearity was found. The final model shows good discriminative ability (c-statistic 0·75, SFigure II) and excellent calibration (Hosmer–Lemeshow P=0.54, SFigure III).

In order to produce estimates for the same population, only patients included in the benefit analysis were included in the risk analysis: 51 (1·6 %) had sICH, including 1% and 2·2% in the low-dose and standard-dose alteplase groups, respectively. Patients with sICH were significantly more likely to be older, with a severe neurological deficit, and with history of co-morbidities (including hypertension, previous stroke, coronary artery disease, DM, and AF) and prior use of aspirin at baseline (Stable 2). The final model includes systolic BP, AF and randomised dose arm (Table 2), and demonstrates good discrimination (c-statistic 0·71, SFigure II) and excellent calibration (Hosmer–Lemeshow P=0.44, SFigure III). No collinearity or interactions were found.

Model validation and performance

There were 1526 (29.5% were treated by low-dose alteplase) patients included in the analysis from the acute stroke registry dataset. The benefit model demonstrated both good discrimination(C-statistic: 0.76) and calibration (Hosmer–Lemeshow P=0.30). The risk model demonstrated moderate discrimination (0.62) and good calibration (P=0.83) ~~Both the benefit and risk model demonstrated good discrimination (C-statistic: 0.76 and 0.62, respectively;~~(SFigure IV). ~~and~~

calibration (Hosmer–Lemeshow P=0.30 and P=0.83, respectively). Predicted and observed probabilities of the outcomes in the validation data set corresponded well to over one tenth of predicted probability (Figure 1).

Net advantage from low-dose alteplase according to patient characteristics

AIS patients had a net advantage from low-dose alteplase when they were younger, had lower systolic BP, mild neurological deficit, and no AF, DM or pre-morbid symptoms (mRS=1) (Table 3). In the validation cohort, those with a net advantage had the same combination of characteristics to the development cohort (Table 3). When benefit and risk were assigned different weight, results followed a similar pattern (STable 3).

Discussion

The present analysis from ENCHANTED, the only large-scale randomised evaluation of different doses of intravenous alteplase for the treatment of AIS, demonstrates that patient-specific characteristics may determine the anticipated individual effects of low-dose alteplase in terms of benefits of an excellent outcome (mRS 0-1 at 90 days) and increased risk of sICH. The model demonstrated good discriminative ability and was well calibrated when externally validated in the nationwide acute stroke registry dataset from South Korea. Low-dose alteplase appears optimal in younger patients who have lower systolic BP, mild neurological deficit, and an absence of major cardiovascular co-morbidities or pre-morbid symptoms.

A risk-benefit algorithm was generated from the ENCHANTED trial, where the percentage of excellent outcome (mRS 0-1) was 48·9% and 46.8% in the randomised low-dose and standard-dose alteplase groups, respectively, but where low-dose alteplase reduced the risk of sICH significantly by 52% according to the SITS-MOST definition. However, this information pertains to group level and it is not informative over the choice of dose of alteplase at an individual patient level. Furthermore, important secondary analyses failed to identify any patient subgroup that can clearly benefit from low-dose alteplase. Our approach, therefore, was to develop a risk score that incorporated multiple patient-specific variables, in order to determine the balance of benefit and risk for an individual patient according to a combination of characteristics.

Our analyses confirm that age, systolic BP, neurological severity, co-morbid AF and DM, and pre-morbid symptoms, are important factors that influence outcome in thrombolysis-treated AIS patients;(15-17) these factors also form components of established risk scores.(18),(19) More specifically, we have shown a net advantage from low-dose alteplase for younger patients with a normal level of systolic BP (i.e. <140mmHg), mild neurological deficit (i.e. score <10 on NIHSS), and no AF, DM or pre-morbid symptoms; factors which are known to predict good functional outcome and lower risk of sICH after AIS.(17, 20, 21) It is possible that mild AIS patients with a favourable risk profile and inherently favourable prognosis simply benefit from a reduced risk of sICH when they are treated with low-dose alteplase. However, they may also be less likely to have greater ischaemic deficit from large vessel occlusions that are more resistant to low- compared with standard-dose alteplase, thus avoiding the potential reduced lytic efficacy associated with under treatment.

Following on, there are plausible reasons that low-dose alteplase was less effective in severe AIS patients with an unfavourable risk profile, in this case those who were older, had higher systolic BP, severe neurological impairment, co-morbid AF and DM, and pre-morbid symptoms. This may again reflect stroke aetiology; those with higher risk profiles are more likely to have large vessel occlusion and/or greater thrombus length where low-dose alteplase is potentially less effective in achieving recanalization.(8, 22) They may therefore be subject to excess harm from the sequelae of failed recanalization such as infarct extension, cerebral oedema and need for decompressive hemicraniectomy, despite lower rates of sICH. We did not have access to neuroimaging data on these factors in the present analyses, and future analysis of the brain images acquired from participants in ENCHANTED (5000+ scans) may confirm or refute this hypothesis.

In regard to BP, observational data from the SITS registry (23, 24) revealed that high systolic BP post-thrombolysis is associated with sICH and poor outcome.(23) In particular, the most favourable outcome was in those with systolic BP levels of 141-150 mmHg between 2–24 hours after thrombolysis.(24) Systolic BP was an important factor in our risk-benefit model, but not in a way that one might initially anticipate; patients at higher risk of sICH due to elevated BP did not benefit from low-dose alteplase. Instead, the present model suggests patients with favourable characteristics that include lower systolic BP had greater net advantage from low-dose alteplase. This is due to the characteristics being considered in combination rather than individually. The ongoing ENCHANTED BP arm(6) will provide insight as to whether more intensive BP lowering (systolic target 130-140 mmHg) has superior efficacy and lower risk of ICH compared to longstanding guideline recommendations (systolic target <180 mmHg) in the context of thrombolysis in AIS.

Interpretation of the present model should be done in the context of the original trial, where, in the primary group-level analyses, low-dose alteplase was not shown to be non-inferior to standard-dose, nor did it perform significantly well in a particular subgroup according to single patient characteristics.(7-10, 25) The novel value of the current predictive model arises from the use of a combination of clinically significant and routinely available patient characteristics that constitute a profile for which low-dose alteplase confers a net advantage. The potential utility of low-dose alteplace in this context has scientific plausibility through the mechanisms discussed above, and furthermore, was externally validated using real-world registry data. However, there was much less sICH in ENCHANTED according to SITS-MOST criteria compared with that in the stroke registry using a comparable but less specific criteria. Therefore, the risk model performs less optimistically due to lower discriminative ability. This is an unavoidable limitation of comparing clinical trial definitions with those applied to registries. It is also worth noting that the majority of participants in ENCHANTED were Asian, and the model was validated in a Korean cohort, thus its applicability to other groups in unknown.

In conclusion, the beneficial effects of low-dose alteplase in the individual patient, in terms of improving the probability of excellent outcome (mRS 0-1) and reducing the risk of sICH, can be quantified using a multivariable risk algorithm. Low-dose alteplase appears optimal in patients with mild AIS and a favourable risk profile. Future studies should aim to determine the effects of low-dose vs. standard dose alteplase in subgroups according to neuroimaging characteristics, such as thrombus burden and infarct volume, as well as associations of low-dose alteplase with subsequent infarct extension, cerebral edema and hemicraniectomy. — These findings may also support future research that focuses on low-dose thrombolysis in mild AIS patients, for example in those who are not eligible for mechanical thrombectomy.

Contributors

XW undertook the analyses and wrote the first and subsequent drafts of report; TM, QL, CA, and MW interpreted the data and wrote the first draft of the report; TR, CA, RL and JC obtained funding, planned and supervised the study; all other authors provided critical review of the report.

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Figure legends

Figure 1 Predicted vs. observed probabilities of outcomes in the validation model

Table 1 Final predictive model for benefit* at 90 days

	Estimate	SE	P value
Age (years)	-0.0117	0.00355	0.001
Systolic BP (mmHg)	-0.00598	0.00204	0.003
NIHSS score			
0-4	Ref		
5-10	-0.9667	0.1102	<0.0001
11-15	-1.9048	0.1299	<0.0001
≥16	-2.4569	0.1431	<0.0001
Atrial fibrillation	1.3955	0.6471	0.031
Diabetes mellitus	-0.2604	0.0996	0.009
No significant disability (mRS=1)	-0.7921	0.1089	<0.0001
Randomised to low-dose alteplase treatment	-0.1443	0.0788	0.067
Age*atrial fibrillation	-0.0238	0.00905	0.009

BP: blood pressure; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scale; SE: standard error

* defined according to scores 0-1 on the mRS at 90-days

Table 2: Final predictive model for the risk of symptomatic intracranial haemorrhage*

	Estimate	SE	P value
Systolic BP (mmHg)	0.0206	0.007	0.009
Atrial fibrillation	1.3316	0.287	<0.000
Randomised to low-dose alteplase treatment	-0.8018	0.305	0.009

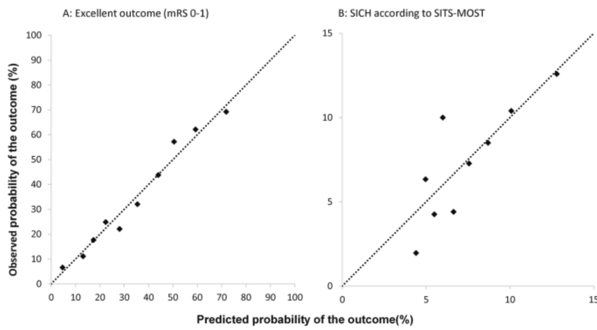
BP: blood pressure; SE: standard error

*defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)

Table 3 Patient characteristics by net advantage from low-dose alteplase

Net advantage from low-dose alteplase	**Development cohort**		**Validation cohort**	
	No (n=339, 11%)	**Yes (n=2858, 89%)**	**No (n=363, 24%)**	**Yes (n=1162, 76%)**
Age, years	75(10.4)	66(12.7)	74(10.3)	66(12.5)
Systolic BP, mmHg	160(14.8)	148(19.9)	164(26.3)	143(26.1)
NIHSS	16(10-20)	8(5-13)	16(12-20)	9(5-14)
Pre-stroke mRS=0	211(62.2%)	2393(83.7%)	236(65.0%)	1044(89.9%)
Atrial fibrillation	330(97.4%)	294(10.3%)	322(88.7%)	302(26.0%)
Diabetes mellitus	76(22.4%)	549(19.2%)	104(28.7%)	267(22.9%)

BP: blood pressure; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke Scale



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