Influence of renal impairment on outcome for thrombolysis-treated acute ischemic stroke: ENCHANTED post-hoc analysis

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Abstract

**Background and purpose:** Renal dysfunction (RD) is associated with poor prognosis following stroke. We assessed the effects of RD on outcomes and interaction with low- versus standard-dose alteplase in a post-hoc subgroup analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED).

**Methods:** 3220 thrombolysis-eligible patients with acute ischemic stroke (AIS) (mean age 66.5 years, 37.8% female) were randomly assigned to low-dose (0.6mg/kg) or standard-dose (0.9mg/kg) intravenous alteplase within 4.5 hours of symptom onset. 659 (19.8%) patients had moderate-to-severe RD (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m$^2$) at baseline. The impact of RD on death or disability (modified Rankin scale [mRS] scores 2 to 6) at 90-days, and symptomatic intracerebral hemorrhage (sICH), was assessed in logistic regression models.

**Results:** Compared to patients with normal renal function (>90ml/min/1.73m$^2$), those with severe RD (<30ml/min/1.73m$^2$) had increased mortality (adjusted odds ratio [OR] 2.07, 95% confidence intervals [CI] 0.89-4.82; p=0.04 for trend); every 10ml/min/1.73m$^2$ lower eGFR was associated with an adjusted 9% increased odds of death from thrombolysis-treated AIS. There was no significant association with mRS scores 2-6 (1.03, 0.62-1.70; p=0.81 for trend), mRS 3-6 (1.20, 0.72-2.01; p=0.44 for trend) or sICH, nor any heterogeneity in comparative treatment effects between low-dose and standard-dose alteplase by RD grades.

**Conclusions:** RD is associated with increased mortality but not disability or sICH in thrombolysis-eligible and treated AIS patients. Uncertainty persists as to whether low-dose alteplase confers benefits over standard-dose in AIS patients with RD.

**Clinical Trial Registration:** Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01422616
Patients with renal dysfunction (RD) have increased risk of ischemic and hemorrhagic stroke, with increased stroke severity and poor outcome.\(^1\) Whilst guidelines acknowledge uncertainty over the safety and efficacy of intravenous alteplase in acute ischemic stroke (AIS) patients with a clinical history of potential bleeding diathesis or coagulopathy, not specific to RD,\(^2\) concerns over excessive bleeding contributes to under-utilization of intravenous thrombolysis in patients with AIS and RD. Nonetheless, a recent systematic review and meta-analysis of 14 observational studies involving 53,553 patients showed no increase in poor outcome or symptomatic intracerebral hemorrhage (sICH).\(^3\) However, these data are dominated by two large multi-center cohort studies\(^4,5\) with few Asian patients who are considered at high sICH risk\(^6\) and where lower doses (0.6mg/kg) of intravenous alteplase are often preferentially used.\(^7\) The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) compared the effectiveness of low-dose versus standard-dose intravenous alteplase.\(^8\) Herein, we report a post-hoc subgroup analysis to determine the prognostic significance of RD and its potential modification of the effects of alteplase.

**Methods**

ENCHANTED is an international, multicenter, prospective, factorial, randomized, open-label, blinded-endpoint trial; the details of which are outlined elsewhere.\(^8\) In brief, 3310 patients with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for thrombolysis, including symptom onset within 4.5 hours, 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. Renal function was derived on serum creatinine obtained at presentation in 3220 (97.3%) patients with data available. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epidemiology Collaboration equation\(^9\); stages of renal function classified as G\(_1\) reflecting ‘normal’ renal function (eGFR \(\geq\)90ml/min/1.73m\(^2\)), G\(_2\) ‘mildly reduced’ (60-89), G\(_3\) ‘moderately reduced’
(30-59), G4 ‘severely reduced’ (15-29), and G5 ‘end-stage’ (<15) renal dysfunction. Stroke severity was measured using the Glasgow coma scale and the National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, and at day 7 (or hospital discharge). Uncompressed digital images of all baseline and follow-up brain imaging were collected and analyzed centrally for any intracranial hemorrhage by independent assessors blind to clinical data, treatment, and date and sequence of scan (see Supplemental Materials).

The primary clinical outcome was the combined endpoint of death or disability at 90 days, defined by scores of 2 to 6 on the modified Rankin scale (mRS). Secondary outcomes and statistical analyses are described in the Supplemental Materials.

Results

This post-hoc subgroup analysis included 3220 patients (mean age 66.5 years, 37.8% female) where assessment of renal function was available on hospital admission, of whom 659 (19.8%) had moderate-to-severe RD (eGFR <60ml/min/1.73m²; mean [SD] 43.6 [14.4ml], range 2.93 to 59.98). Compared to patients with normal or only mildly reduced renal function, a greater percentage of patients with at least moderate RD were female, of non-Asian ethnicity, had concomitant co-morbidity, associated statin and aspirin therapy, and reduced pre-morbid functional ability (Table 1, Supplemental Table I). Patients with stages 3 and 4 RD were thrombolyzed earlier after symptom onset; other differences in management are reported in Supplemental Table II.

As a continuous variable, lower eGFR was associated with increased odds of death within 90 days; every 10 ml/min/1.73m² lower eGFR was associated with a significant 9% increased odds of 90-day mortality (Supplemental Table III). Overall, there was more than a two-fold greater odds of death in patients with eGFR <30 ml/min/1.73m² compared to those with normal renal function (adjusted OR [aOR] 2.07, 95%CI 0.89-4.82; P=0.04 for trend) (Supplemental Table IV); many causes of death being potentially reversible (Supplemental
Table V). With respect to the combined outcome of death and disability, patients with a lower eGFR did not have an increased odds of a poor outcome, whether defined by 90-day mRS scores 2 to 6 (aOR 1.03, 95%CI 0.62-1.70; P=0.81 for trend) or scores 3 to 6 (aOR 1.20, 95%CI 0.72-2.01; P=0.44 for trend) (Supplemental Table IV). No significant difference was observed in neurological deterioration, defined as NIHSS increase by 4 or more points at 24 hours: eGFR stage 1 (6.7%), 2 (8.3%), 3 (9.4%), 4 (11.1%) and 5 (8.3%). There was no association between renal dysfunction and sICH, although the numbers were low (Supplemental Table VI).

There was no significant difference in the main efficacy outcomes between both alteplase doses in patients with eGFR Stages G4 and G5, whether defined by 90-day dichotomized mRS or mortality (Supplemental Table VII), or by ordinal shift in the mRS (Figure). Finally, sICH was infrequent with no significant difference between low-dose and standard-dose alteplase, and no fatal ICH in patients with eGFR <30 ml/min/1.73m² who received low-dose alteplase (Table 2).

**Discussion**

In keeping with previous studies, this post-hoc subgroup analysis of the ENCHANTED trial confirmed an increased risk of death, but no increase in poor functional outcome after adjustment for confounding factors in patients with AIS and RD who were eligible for and received intravenous alteplase. Patients with an eGFR of <30 ml/min/1.73m² had twice the mortality as those with moderately impaired or normal renal function. However, this increased mortality risk did not appear to be due to an excess of sICH, and although this finding is likely underpowered, is apparently related to indirect causes such as pneumonia, sepsis, and non-vascular events, in keeping with the findings of other studies.5,7,11 Accordingly, clinicians should be vigilant towards the prevention and treatment of infectious and venous thromboembolic complications in these patients.
Several observational studies have previously reported on AIS patients treated with low-dose alteplase, and on the associations of low eGFR with stroke outcomes, these findings have been limited and inconclusive. Our post-hoc subgroup analysis of ENCHANTED provides the first randomized comparison of low- versus standard-dose alteplase on stroke outcomes in this important patient subgroup. Although the findings are not conclusive, they suggest that RD should not be regarded as a definite contraindication to thrombolysis in otherwise eligible patients, especially due to concerns of an increased sICH risk, in accord with recent guidelines.

Strengths of this study include the prospective design with high rates of follow-up, treatment adherence, and rigorous independent assessment of outcomes in a large sample of both non-Asian and Asian patients recruited in different healthcare settings. However, these analyses were undertaken in a clinical trial population of predominantly mild-to-moderate severity AIS, and some bias may relate to the categorization of RD from a single measurement of creatinine undertaken between hospital admission and randomization, and the definitions of RD that normally require the persistence of eGFR <60 ml/min/1.73m² for 3 months or more in the absence of a reversible condition, such as volume depletion. Admission eGFR may have been confounded from acute illness, or sepsis, and only limited information was obtained on a patient’s medical history and condition, although the likelihood that a high proportion of patients requiring renal replacement therapy seems unlikely. Finally, we may have overlooked important differences between the extremes of RD by combining patients with eGFR <30ml/min/1.73m² to increase the efficiency of analyses.

Conclusions

Our evaluation of the ENCHANTED trial indicates that RD is associated with increased mortality in thrombolysis-treated AIS patients. However, RD did not increase the likelihood of a poor functional outcome, nor was it associated with high risk of sICH. Thus, RD per se
does not appear to be an absolute contraindication to alteplase use, although the sICH risk may be underestimated in this underpowered post-hoc analysis of predominantly mild-to-moderate stroke AIS patients with RD. In addition, uncertainty persists as to whether low-dose alteplase confers benefits over standard-dose in this patient group.
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