Influence of Renal Impairment on Outcome for Thrombolysis-Treated Acute Ischemic Stroke

ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) Post Hoc Analysis

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Background and Purpose—Renal dysfunction (RD) is associated with poor prognosis after 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 ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study).

Methods—A total of 3220 thrombolysis-eligible patients with acute ischemic stroke (mean age, 66.5 years; 37.8% women) were randomly assigned to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) intravenous alteplase within 4.5 hours of symptom onset. Six hundred and fifty-nine (19.8%) patients had moderate-to-severe RD (estimated glomerular filtration rate, <60 mL/min per 1.73 m^2) at baseline. The impact of RD on death or disability (modified Rankin Scale scores, 2–6) at 90 days, and symptomatic intracerebral hemorrhage, was assessed in logistic regression models.

Results—Compared with patients with normal renal function (>90 mL/min per 1.73 m^2), those with severe RD (<30 mL/min per 1.73 m^2) had increased mortality (adjusted odds ratio, 2.07; 95% confidence interval, 0.89–4.82; P=0.04 for trend); every 10 mL/min per 1.73 m^2 lower estimated glomerular filtration rate was associated with an adjusted 9% increased odds of death from thrombolysis-treated acute ischemic stroke. There was no significant association with modified Rankin Scale scores 2 to 6 (adjusted odds ratio, 1.03; 95% confidence interval, 0.62–1.70; P=0.81 for trend), modified Rankin Scale 3 to 6 (adjusted odds ratio, 1.20; 95% confidence interval, 0.72–2.01; P=0.44 for trend), or symptomatic intracerebral hemorrhage, or 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 symptomatic intracerebral hemorrhage in thrombolysis-eligible and treated acute ischemic stroke patients. Uncertainty persists as to whether low-dose alteplase confers benefits over standard-dose alteplase in acute ischemic stroke patients with RD.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01422616.

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Key Words: glomerular filtration rate ■ hypertension ■ intracranial hemorrhages ■ odds ratio ■ stroke

Patients with renal dysfunction (RD) have increased risk of ischemic and hemorrhagic stroke, with increased stroke severity and poor outcome.[1] While 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

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specific to RD,[2] concerns over excessive bleeding contribute to underutilization 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 2 large multicenter cohort studies[4,5] with few Asian patients who are considered at high sICH risk[6] and where lower doses (0.6 mg/kg) of intravenous alteplase are often preferentially used.[7] The ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) 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-end point 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 (0.6 mg/kg; 15% as bolus, 85% as infusion for 1 hour) or standard-dose (0.9 mg/kg; 10% as bolus, 90% as infusion for 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 Chronic Kidney Disease–Epidemiology Collaboration equation[9]; stages of renal function classified as G_1 reflecting normal renal function (eGFR ≥90 mL/min per 1.73 m^2), G_2 mildly reduced (60–89), G_3 moderately reduced (30–59), G_4 severely reduced (15–29), and G_5 end-stage (≤15) RD.[10] Stroke severity was measured using the Glasgow coma scale and the National Institutes of Health stroke scale 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 online-only Data Supplement).

The primary clinical outcome was the combined end point of death or disability at 90 days, defined by scores of 2 to 6 on the modified Rankin Scale. Secondary outcomes and statistical analyses are described in the online-only Data Supplement.

Results

This post hoc subgroup analysis included 3220 patients (mean age, 66.5 years; 37.8% women) where assessment of renal function was available on hospital admission, of whom 659 (19.8%) had moderate-to-severe RD (eGFR <60 mL/min per 1.73 m^2; mean [SD], 43.6 [14.4 mL]; range, 2.93–59.98). Compared with patients with normal or only mildly reduced renal function, a greater percentage of patients with at least moderate RD were women, of non-Asian ethnicity, had concomitant comorbidity, associated statin and aspirin therapy, and reduced pre-morbid functional ability (Table 1; Table I in the online-only Data Supplement). Patients with stages 3 and 4 RD were thrombolyzed earlier after symptom onset; other differences in management are reported in Table II in the online-only Data Supplement.

As a continuous variable, lower eGFR was associated with increased odds of death within 90 days; every 10 mL/min per 1.73 m^2 lower eGFR was associated with a significant 9% increased odds of 90-day mortality (Table III in the online-only Data Supplement). Overall, there was more than a 2-fold greater odds of death in patients with eGFR <30 mL/min per 1.73 m^2 compared with those with normal renal function (adjusted odds ratio, 2.07; 95% confidence interval, 0.89–4.82; P=0.04 for trend; Table IV in the online-only Data

Table 1. Selected Baseline Characteristics by Estimated Glomerular Filtration Rate

	eGFR Category, mL/min per 1.73 m^2					
	Stage G_1 (n=1171) ≥90	Stage G_2 (n=1390) 60–89	Stage G_3 (n=556) 30–59	Stage G_4 (n=54) 15–29	Stage G_5 (n=49) ≤15	*P* Trend
Time from stroke onset to randomization (h), mean (SD)	2.87 (0.91)	2.68 (0.92)	2.55 (0.97)	2.59 (0.86)	2.70 (1.02)	<0.001
Female, n (%)	397/1171 (33.9)	508/1390 (36.6)	259/556 (46.6)	27/54 (50.0)	25/49 (51.0)	<0.001
Age (y), mean (SD)	58.1 (10.9)	69.7 (11.0)	75.6 (10.3)	76.6 (12.0)	64.4 (14.7)	<0.001
Ethnicity, n (%)						<0.001
Non-Asian	255/1171 (21.8)	552/1390 (39.7)	307/556 (55.2)	37/54 (68.5)	24/49 (49.0)	
Asian	916/1171 (78.2)	838/1390 (60.3)	249/556 (44.8)	17/54 (31.5)	25/49 (51.0)	
Clinical features						
Systolic BP, mm Hg, mean (SD)	149 (20)	150 (20)	148 (21)	150 (22)	149 (19)	0.56
Diastolic BP, mm Hg, mean (SD)	87 (12)	84 (13)	81 (13)	81 (14)	85 (13)	<0.001
NIHSS score						
Median (Q1–Q3)	8 (4–12)	8 (5–14)	10 (6–16)	8 (5–16)	8 (6–11)	<0.001
Previous stroke, n (%)	167/1171 (14.3)	272/1390 (19.6)	108/556 (19.4)	14/54 (25.9)	10/49 (20.4)	0.001
Randomized to low-dose treatment	573 (48.9)	704 (50.7)	271 (48.7)	32 (59.3)	24 (49.0)	0.57

Data are mean (SD) or median (interquartile interval). Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; and NIHSS, National Institutes of Health stroke scale.

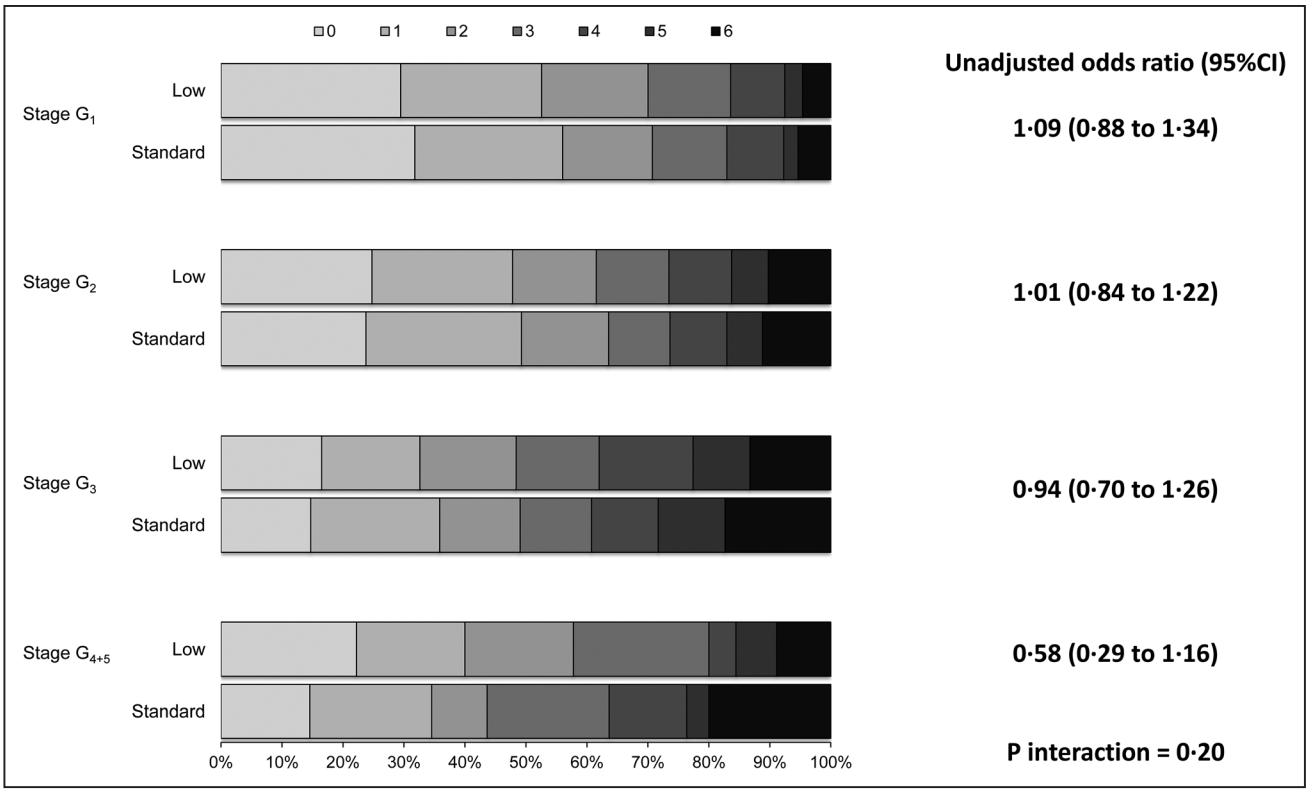

Figure. Global functional outcome at 90 days in patients by estimated glomerular filtration rate and randomized treatment. The figure shows the raw distribution of scores on the modified Rankin Scale at 90 days with scores ranging from 0 to 6, as fully described in the online-only Data Supplement, along with grades of renal dysfunction. CI indicates confidence interval.

Supplement); many causes of death being potentially reversible (Table V in the online-only Data Supplement). 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 modified Rankin Scale scores 2 to 6 (adjusted odds ratio, 1.03; 95% confidence interval, 0.62–1.70; *P*=0.81 for trend) or scores 3 to 6 (adjusted odds ratio, 1.20; 95% confidence interval, 0.72–2.01; *P*=0.44 for trend; Table IV in the online-only Data Supplement). No significant difference was observed in neurological deterioration, defined as National Institutes of Health stroke scale increase by ≥4 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 RD and sICH although the numbers were low (Table VI in the online-only Data Supplement).

There was no significant difference in the main efficacy outcomes between both alteplase doses in patients with eGFR stages G_4 and G_5, whether defined by 90-day dichotomized modified Rankin Scale or mortality (Table VII in the online-only Data Supplement) or by ordinal shift in the modified Rankin Scale (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 per 1.73 m^2 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[3–5] in patients with AIS and RD who were eligible for and received intravenous alteplase. Patients with an eGFR of <30 mL/min per 1.73 m^2 had twice the mortality as those with moderately impaired or normal renal function. However, this increased mortality risk did not seem to be because of an excess of sICH, and although this finding is likely underpowered, is apparently related to indirect causes, such as pneumonia, sepsis, and nonvascular events, in keeping with the findings of other studies.[5,7,11] Accordingly, clinicians should be vigilant toward the prevention and treatment of infectious and venous thromboembolic complications in these patients.

Several observational studies have previously reported on patients with AIS treated with low-dose alteplase, and on the associations of low eGFR with stroke outcomes, these findings have been limited and inconclusive.[7,12,13] 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 because of concerns of an increased sICH risk, in accord with recent guidelines.[2]

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

Table 2. Symptomatic Intracerebral Hemorrhage by Estimated Glomerular Filtration Rate and Randomized Treatment

	eGFR, mL/min per 1.73 m^2			
	Stage G_1 (n=1171)	Stage G_2 (n=1390)	Stage G_3 (n=556)	Stage G_{4+5} (n=103)
Criteria	n/N (%)	n/N (%)	n/N (%)	n/N (%)
SITS-MOST				
Low dose	4/598 (0.7)	10/686 (1.5)	3/285 (1.1)	0/47 (0.0)
Standard dose	8/573 (1.4)	17/704 (2.4)	6/271 (2.2)	1/56 (1.8)
NINDS				
Low dose	25/598 (4.2)	49/686 (7.1)	22/285 (7.7)	2/47 (4.3)
Standard dose	34/573 (5.9)	64/704 (9.1)	26/271 (9.6)	2/56 (3.6)
ECASS2				
Low dose	13/598 (2.2)	28/686 (4.1)	13/285 (4.6)	1/47 (2.1)
Standard dose	22/573 (3.8)	42/704 (6.0)	18/271 (6.6)	1/56 (1.8)
ECASS3				
Low dose	5/598 (0.8)	11/686 (1.6)	4/285 (1.4)	0/47 (0.0)
Standard dose	10/573 (1.8)	21/704 (3.0)	7/271 (2.6)	1/56 (1.8)
IST-3				
Low dose	8/598 (1.3)	15/686 (2.2)	9/285 (3.2)	1/47 (2.1)
Standard dose	13/573 (2.3)	26/704 (3.7)	8/271 (3.0)	1/56 (1.8)
Clinician reported				
Low dose	36/598 (6.0)	68/686 (9.9)	28/285 (9.8)	3/47 (6.4)
Standard dose	35/573 (6.1)	72/704 (10.2)	34/271 (12.6)	5/56 (8.9)
Fatal ICH				
Low dose	3/598 (0.5)	4/686 (0.6)	2/285 (0.7)	0/47 (0.0)
Standard dose	5/573 (0.9)	9/704 (1.3)	6/271 (2.2)	1/56 (1.8)
Adjudicated any ICH				
Low dose	73/598 (12.2)	132/686 (19.2)	62/285 (21.8)	5/47 (10.6)
Standard dose	82/573 (14.3)	138/704 (19.6)	54/271 (19.9)	12/56 (21.4)
Any ICH				
Low dose	85/598 (14.2)	150/686 (21.9)	63/285 (22.1)	6/47 (12.8)
Standard dose	91/573 (15.9)	155/704 (22.0)	62/271 (22.9)	12/56 (21.4)

ECASS indicates European Cooperative Acute Stroke Study; eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; IST, International Stroke Trial; NINDS, National Institute of Neurological Disorders and Stroke; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study.

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 per 1.73 m^2 for ≥3 months in the absence of a reversible condition, such as volume depletion.[14] 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 <30 mL/min per 1.73 m^2 to increase the efficiency of analyses.

Conclusions

Our evaluation of the ENCHANTED trial indicates that RD is associated with increased mortality in thrombolysis-treated patients with AIS. However, RD did not increase the likelihood of a poor functional outcome or was it associated with high risk of sICH. Thus, RD per se does not seem 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 alteplase in this patient group.

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