Supplemental Material

Supplemental Methods

Data on all patients (n=721) from 2 randomized trials of alteplase versus placebo or open control for AIS were excluded from our analysis. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET; n=101) was excluded because patient selection did not follow European regulatory criteria for thrombolysis with alteplase (patients who had comorbid neurological disorders and/or were unable to undergo MRI scanning were excluded).[1] The European Cooperative Acute Stroke Study (ECASS) 1 (n=620) was excluded because patients received alteplase at a dose of 1.1 mg/kg rather than 0.9 mg/kg as approved in Europe.[2]

Supplemental Results

Baseline characteristics of the full RCT population and age-based subgroups who met European regulatory criteria (excluding upper age restriction)

Baseline demographic and disease characteristics are presented in Supplemental Table I. Patients aged >80 years had more severe strokes than did younger patients (mean [SD] baseline NIHSS score 13.2 [6.3] versus 11.2 [5.7]). A greater proportion of females (637/1028 [62.0%] versus 936/2405 [38.9%]), lower mean (SD) body weight (67.0 [12.9] versus 77.5 [15.8] kg) and higher rates of pre-existing hypertension (710/1028 [69.1%] versus 1397/2405 [58.1%]), atrial fibrillation (428/1028 [41.6%] versus 395/2405 [16.4%]), and previous stroke (226/1028 [22.0%] versus 313/2405 [13.0%]) were observed in patients aged >80 years versus the younger subgroup. Mean (SD) time to treatment was slightly shorter in the elderly versus younger subgroup (187.3 [48.6] versus 205.0 [55.5] minutes, respectively).

Baseline characteristics of the full SITS-UTMOST Registry population and age-based subgroups who met European regulatory criteria (excluding upper age restriction)

Patients aged >80 years, who otherwise met existing European regulatory criteria experienced more severe strokes than did younger patients (mean [SD] baseline NIHSS scores 12.9 [6.3] versus 11.0 [6.1], respectively). Patients aged >80 years also had a greater proportion of females (1401/2420 [57.9%] versus 3969/9491 [41.8%]), lower mean (SD) body weight (70.0 [13.0] versus 78.5 [15.3] kg), and higher rates of pre-existing hypertension (1817/2420 [75.1%] versus 5807/9491 [61.2%]), atrial fibrillation (834/2420 [34.5%] versus 1652/9491 [17.4%]), and previous stroke (289/2420 [11.9%] versus 846/9491 [8.9%]) compared with younger patients. Mean (SD) time to treatment was similar in both age subgroups (151.1 [50.4] mins aged >80 years versus 152.5 [51.9] mins aged ≤80 years).

Supplemental References

1. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299-309
2. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;274:1017-1025

Supplemental Table I. Baseline Demographic Characteristics of Patients in the Full RCT Population and Age-Defined Subgroups Who Met European Regulatory Criteria

Characteristic	Full RCT population		Specified subgroups*			
			Met European regulatory criteria, aged ≤80 years		Met European regulatory criteria other than aged >80 years	
	Alteplase (n=3026)	Placebo (n=3009)	Alteplase (n=1182)	Placebo (n=1223)	Alteplase (n=518)	Placebo (n=510)
Sex, n (%)						
Male	1638 (54.1)	1612 (53.6)	723 (61.2)	746 (61.0)	206 (39.8)	185 (36.3)
Missing	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age (years), mean (SD)	71.8 (13.1)	71.5 (13.2)	65.5 (11.3)	65.9 (11.0)	85.9 (4.0)	86.0 (4.0)
Age subset (years), n (%)						
≤80	2162 (71.4)	2174 (72.2)	1182 (100.0)	1223 (100.0)	0 (0.0)	0 (0.0)
>80	864 (28.6)	835 (27.8)	0 (0.0)	0 (0.0)	518 (100.0)	510 (100.0)
Body weight (kg), mean (SD)	74.4 (15.6)	75.2 (16.1)	77.0 (15.2)	77.9 (16.4)	67.1 (13.2)	66.9 (12.6)
NIHSS at baseline, mean (SD)	11.9 (6.7)	12.0 (6.5)	10.9 (5.5)	11.5 (5.8)	13.3 (6.4)	13.2 (6.3)
Time from stroke onset to treatment (mins), mean (SD)	238.3 (74.2)	237.6 (74.1)	205.3 (55.6)	204.8 (55.4)	185.3 (49.0)	189.3 (48.2)
History of diabetes mellitus, n (%)						
Yes	483 (16.0)	491 (16.3)	177 (15.0)	174 (14.2)	32 (6.2)	27 (5.3)
Missing	2 (0.1)	3 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
History of stroke, n (%)						
Yes	575 (19.0)	574 (19.1)	144 (12.2)	169 (13.8)	115 (22.2)	111 (21.8)
Missing	4 (0.1)	8 (0.3)	1 (0.1)	5 (0.4)	0 (0.0)	0 (0.0)

History of hypertension, n (%)						
Yes	1876 (62.0)	1863 (61.9)	687 (58.1)	710 (58.1)	348 (67.2)	362 (71.0)
Missing	2 (0.1)	7 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
History of atrial fibrillation, n (%)						
Yes	748 (24.7)	711 (23.6)	193 (16.3)	202 (16.5)	217 (41.9)	211 (41.4)
Missing	4 (0.1)	2 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline blood glucose level (mg/dL), mean (SD)[†]	137.2 (54.4)	135.5 (53.2)	138.0 (56.4)	134.9 (51.4)	130.6 (40.3)	128.8 (39.3)
Missing	418	403	384	361	10	5

NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial.

*Two subgroups of patients who met European regulatory criteria (excluding upper age restriction) were specified based on age.

[†]Baseline blood glucose level not recorded in ECASS-3.