

1 Low-dose versus standard-dose alteplase for stroke in the ENCHANTED trial: searching
2 for subgroup benefit

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57 **Short title:** Role of age, ethnicity, and severity on outcome in the ENCHANTED trial

58 **List of table and figures**

59 **Tables: 1**

60 **Figures: 3**

61 **Supplemental Tables: 19**

62 **Supplemental Figures: 2**

63

64 **Itemized list of tables and figures:**

65 Table 1 Baseline characteristics by age groups

66 Figure 1 Randomized treatment effects on death or disability at 90 days by age, ethnicity, and
67 stroke severity

68 Figure 2 Randomized treatment effects on symptomatic intracerebral hemorrhage by (A) age,
69 (B) ethnicity, and (C) stroke severity

70 Figure 3 Randomized treatment effects on functional outcome according to the modified Rankin
71 scale at 90 days, by ethnicity

72

73 **Keywords:** thrombolysis, alteplase, acute ischemic stroke, symptomatic intracerebral
74 hemorrhage, age, ethnicity, stroke severity

75 **Key points**

76 **Question** Does low-dose (0.6mg/kg) offer benefits over standard-dose (0.9mg/kg) intravenous
77 alteplase in older, Asian, or severely affected patients with acute ischemic stroke (AIS)?

78 **Finding** There are no clear differential benefits of low-dose compared to standard-dose alteplase
79 on disability outcomes according to age, ethnicity, and neurological severity, but a lower risk of
80 symptomatic intracerebral hemorrhage for low-dose alteplase was consistent across these
81 subgroups of AIS patients. Increasing age and neurological severity, but not ethnicity, are
82 associated with increased risks of death or disability following AIS in treated thrombolysis-
83 eligible patients.

84 **Meaning** Decisions about using a lower dose of alteplase for use in thrombolysis-eligible AIS
85 patients should not be based solely on age, ethnicity, or neurological severity.

86

87 **Abstract**

88 **Importance** A lower dose of intravenous alteplase appears to be a safer treatment, with reduced
89 risk of symptomatic intracerebral hemorrhage (sICH) compared to standard-dose alteplase, but
90 there is uncertainty over how this effect translates into overall clinical benefit in patients with
91 acute ischemic stroke (AIS).

92 **Objectives** To assess whether older, Asian, or severely affected AIS patients, who are often
93 considered at high risk of thrombolysis, may benefit more from low-dose compared to standard-
94 dose alteplase treatment.

95 **Design, Setting, and Participants** Data are from the Enhanced Control of Hypertension and
96 Thrombolysis Stroke Study (ENCHANTED), an international, randomized, open-label, blinded-
97 endpoint trial of low- (0.6mg/kg) versus standard-dose (0.9mg/kg) intravenous alteplase in AIS
98 patients.

99 **Main Outcomes and Measures** The primary endpoint was a poor outcome defined by the
100 combination of death or any disability (modified Rankin scale [mRS] scores 2-6 at 90 days).
101 Secondary outcomes were sICH (defined by various standard criteria) and different measures of
102 disability outcome on the mRS. Interaction of the treatment effects were investigated across pre-
103 specified patient characteristic subgroups of age, ethnicity (Asian versus non-Asian), and
104 severity (defined by National Institutes of Health Stroke Scale scores).

105 **Results** In 3297 patients (1248 female, mean age 67 [SD 13] years), no significant differences
106 between the treatment effects of low- versus standard-dose alteplase were observed for various
107 disability outcomes (death or disability, ordinal shift of mRS, or death alone) by age, ethnicity or
108 severity. With respect to sICH, there were consistent reductions in rates of sICH with low-dose
109 alteplase, although this was not statistically significant, by age, ethnicity or severity.

110 **Conclusions and Relevance** There was no clear superiority of the effects of low-dose versus
111 standard-dose alteplase on death or disability in key demographic subgroups of AIS patients,
112 including ethnicity. Further investigation is required to identify patients who may clearly benefit
113 from low-dose alteplase in AIS.

114 **Trial Registration** The trial is registered with ClinicalTrials.gov (NCT01422616).

115

116 **Introduction**

117 Low-dose intravenous alteplase (0.6mg/kg body weight; maximum 60 mg) was approved in
118 Japan for the treatment of acute ischemic stroke (AIS) within 3 hours of onset. This approval
119 was based on a single arm study, the Japan Alteplase Clinical Trial, showing clinical efficacy
120 and safety of low-dose alteplase in a Japanese population were comparable to use of standard-
121 dose (0.9mg/kg body weight; maximum 90 mg) in other populations.^{1,2} Although the standard
122 dose of 0.9 mg/kg, approved by most other regulatory authorities, has not been comprehensively
123 tested in other Asian countries, clinicians in the region may prefer use of low-dose alteplase
124 because of its lower cost or apparent reduced bleeding risk.^{3,4} Thus, uncertainties remain about
125 the optimal dose of alteplase in Asian populations as observational studies have produced
126 conflicting findings⁵⁻⁸ and there has been an absence of randomized evidence.

127 Recent information from individual patient data of randomized trials or stroke registries about
128 the hazards of intravenous alteplase, and how these relate to benefits in different patient
129 subgroups,⁹⁻¹² show similar proportional benefits of thrombolysis for patients aged 80 years or
130 more, and for those with severe neurological deficit (National Institutes of Health Stroke Scale
131 [NIHSS] scores >25). These data are reflected in the latest guideline recommendations of the
132 American Heart Association (AHA) / American Stroke Association (ASA)¹³ and British Royal
133 College of Physicians.¹⁴ Although there is proven clinical benefit from thrombolysis for older
134 and severe AIS patients, these features increase the risk of symptomatic intracerebral
135 hemorrhage (sICH).¹³ Accordingly, it seems possible that low-dose alteplase may maintain the
136 benefits of treatment whilst reducing sICH risk.

137 In the recently completed alteplase dose evaluation arm of the quasi-factorial Enhanced Control
138 of Hypertension And Thrombolysis Stroke Study (ENCHANTED), use of low-dose alteplase in

139 thrombolysis-eligible AIS patients was not shown to meet the pre-defined non-inferiority margin
140 compared to standard-dose alteplase with respect to the conventional binary clinical endpoint of
141 death and disability, defined by scores of 2-6 on the modified Rankin scale (mRS) at 90 days.
142 However, the study did show that low-dose alteplase was non-inferior for overall functional
143 recovery through ordinal analysis of the mRS and resulted in significantly less sICH, than
144 standard-dose alteplase.^{4,15,16} It is therefore plausible that low-dose alteplase may be a preferable
145 treatment in certain types of patients. Herein, we provide more detailed information about the
146 treatment effects of low- versus standard-dose intravenous alteplase in relation to age, ethnicity
147 (Asian versus non-Asian), and severity of AIS.

148 **Methods**

149 *Participants*

150 The ENCHANTED trial was an international, multi-center, prospective, randomized, open-label,
151 blinded-endpoint trial, the details of which are outlined elsewhere.^{4,15,16} In brief, 3310 patients
152 with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for
153 thrombolysis treatment were included in the alteplase dose arm with random assignment to
154 receive low-dose (0.6mg/kg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose
155 (0.9mg/kg; 10% as bolus, 90% as infusion over 1 hour) intravenous alteplase. The study
156 protocol was approved by the appropriate ethics committee at each participating center, and
157 written informed consent was obtained from each patient or an appropriate surrogate. The study
158 is registered with Clinicaltrials.gov (number NCT01422616).

159 *Procedures*

160 Key demographic and clinical characteristics were recorded at the time of enrolment. Stroke
161 severity was measured using the NIHSS at baseline, 24 hours, and at Day 7 (or earlier on
162 discharge from hospital). Uncompressed digital images of all baseline and follow-up CT, MRI
163 and angiogram images were collected in DICOM format on a CD-ROM identified only with the
164 patient's unique study number, and uploaded by a special purpose-built web-based system for
165 central analysis at The George Institute for Global Health. All brain scans with an intracranial
166 hemorrhage were reviewed by at least two independent assessors, blind to clinical data,
167 treatment, and date and sequence of scan, using MISTar version 3.2 (Apollo Medical Imaging
168 Technology, Melbourne, Victoria, Australia). Assessors graded any hemorrhage as intracerebral,
169 subarachnoid, intraventricular, subdural or other; sICH being graded across all standard
170 definitions (see Supplementary Materials).

171 The primary efficacy outcome in these analyses was that used in the trial, a composite endpoint
172 of death or any disability at 90 days, defined by scores of 2 to 6 on the mRS. Secondary efficacy
173 outcomes included scores of 3 to 6 on the mRS, death alone (mRS 6), and an ordinal analysis of
174 the full range of scores on the mRS. The safety outcome was sICH defined according to several
175 criteria used in other studies.

176 *Statistical Analysis*

177 The treatment effects of low- versus standard-dose alteplase on the disability outcomes and sICH
178 were determined using logistic regression models, and the heterogeneity of the differential effect
179 according to alteplase dose across subgroups estimated by adding an interaction term to the
180 statistical models. Proportional odds regression models were used to determine the treatment
181 effects on the ordinal mRS across subgroups of patients defined by age, ethnicity, and
182 neurological severity; the proportional odds assumption being fulfilled in all the models.^{17,18}

183 Sensitivity analyses were performed using age and baseline NIHSS score as continuous variables
184 in logistic regression models with the same various used for adjustment as described above.

185 The association of age (<50, 50-59, 60-69, 70-79, \geq 80 years), ethnicity (Asian versus non-
186 Asian), and neurological severity (baseline NIHSS 0-4, 5-10, 11-15, 16-21, \geq 22) with death or
187 disability, death, and sICH, were estimated using logistic regression models with adjustment for
188 the baseline covariates (time from onset to randomization [$<$ 3 versus \geq 3 hr], age, sex, ethnicity,
189 baseline systolic blood pressure [SBP], baseline NIHSS score, any history of stroke, coronary
190 artery disease, diabetes mellitus, atrial fibrillation, hypercholesterolemia, pre-morbid mRS [0 or
191 1], and prior use of warfarin anticoagulant, aspirin, or other antiplatelet agent, and randomized
192 treatment [low-dose versus standard-dose]); and additionally for management over the first seven
193 days (SBP at 24 hours, fever occurrence, provision of nasogastric tube feeding, mobilization of a
194 patient by a therapist, and use of compression stockings, intravenous steroids, neurosurgery, and
195 any admission to a stroke unit or intensive care unit, and any rehabilitation or decision to
196 withdraw active care). The heterogeneity of the associations across subgroups was also
197 estimated by adding an interaction term to the model. Data are reported as odds ratios (OR) and
198 95% confidence intervals (CI). Two-sided P values are reported, with $P<0.05$ considered
199 statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for analyses.¹⁵

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201 The funding agencies had no role in the design of the study protocol, in the collection, analysis,
202 or interpretation of the trial data, or in the writing of the manuscript.

203 **Results**

204 *Baseline characteristics and management details*

205 From March 2012 through August 2015, a total of 3310 patients were randomized; 1654 were
206 assigned to low-dose alteplase and 1643 to standard-dose alteplase (after excluding 13 patients: 9
207 with no consent, 1 mistakenly randomized, and 3 with duplicate randomization).¹⁶ All remaining
208 3297 patients (37.8% females; mean age 67 [SD 13] years) were included in the age analyses.

209 Table 1 shows the baseline characteristics of patients by age groups: older patients were
210 significantly more likely to be female, of non-Asian ethnicity, hypertensive, and with a history of
211 co-morbidities and concomitant prior use of aspirin and statin therapy. Additionally, they were
212 more likely to have had strokes of greater neurological severity.

213 There were 3291 patients (2079 Asians and 1212 non-Asians) with available information for
214 ethnicity analyses. Table S1 indicates that non-Asians were significantly older, more likely to be
215 female, had greater co-morbidities (hypertension, atrial fibrillation) and more concomitant use of
216 antihypertensive, warfarin, aspirin, and/or statin therapy, and were treated more quickly with
217 alteplase than Asians (Table S2).

218 Finally, there were 3297 patients (median baseline NIHSS score 8 [interquartile range 5-14])
219 included in the severity analysis. Patients who presented with more severe neurological
220 impairment had similar characteristics to older patients, except that they were more likely to be
221 of Asian ethnicity (Table S3). Differences in the use of alteplase and other management factors
222 over the first seven days post-randomization by age, ethnicity, and stroke severity subgroups, are
223 reported in Tables S4, S2, and S5, respectively.

224 *Effects of low- versus standard-dose alteplase by age, ethnicity, and severity*

225 There was no clear differential effect of alteplase in any particular age group for the disability
226 outcome, whether defined by different cut-points (2 to 6, or 3 to 6) or on an ordinal analysis of
227 the full range of scores on the mRS (all $P \geq 0.51$ for interaction; Figure 1, Tables S6 and S7).

228 Similarly, there was consistency of the lower risk of sICH for low-dose alteplase across age
229 groups (all $P > 0.50$ for interaction; Figure 2A, Table S8).

230 In regard to the comparison of Asian with non-Asian patients, there was no significant difference
231 in the disability outcomes between the two doses of alteplase, whether defined by death or
232 disability (all $P \geq 0.32$ for interaction, Figure 1 and Table S9) or an ordinal analysis of the mRS
233 (Figure 3). Similarly, there was clear beneficial effect of one dose over the other across patients
234 from different regions of the world (China; United Kingdom, continental Europe, or Australia;
235 Asia, other than China; and South America, Figure S1) in relation to the primary outcome.
236 Furthermore, there was no heterogeneity in the differential effect of alteplase dose on the risk of
237 sICH between Asians and non-Asians (Figure 2B and Table S10).¹⁶

238 Finally, the treatment effects of low-dose versus standard-dose alteplase on various disability
239 outcomes (mRS scores 2-6, 3-6, 6 [death], or ordinal analysis) remained consistent across the
240 grades of baseline neurological severity (Figure 1, Tables S11 and S12), even after accounting
241 for treatment delay (Figure S2). There was consistency of the differential treatment effect on the
242 risk of sICH with increasing severity (Figure 2C and Table S13).

243 Prognostic significance of age, ethnicity and neurological severity

244 Older patients were more likely to have a poor outcome (mRS 2-6, 3-6, or death, all $P < 0.01$ for
245 trend, Table S14) but there was no clear association of sICH across a broad range of criteria with
246 increasing age, irrespective of alteplase dose (Table S15). Similarly, there was no significant
247 association between ethnicity and poor outcome (death or disability, Table S16) or sICH (Table
248 S17). However, these endpoints were related to increasing neurological severity of AIS (mRS
249 scores 2-6, 3-6, or 6, all $P < 0.001$ for trend; sICH $P < 0.001$ for trend, according to National
250 Institute of Neurological Disorders and Stroke [NINDS] and the third European Co-operative

251 Acute Stroke Study [ECASS3] criteria), after adjustment for confounders and alteplase dose
252 (Table S18 and S19).

253 **Discussion**

254 In these pre-specified subgroup analyses of the ENCHANTED trial, we found no clear
255 differences in the treatment effects of low-dose versus standard-dose alteplase on the main
256 disability outcomes according to age, ethnicity, and baseline neurological severity in
257 thrombolysis-eligible AIS patients. Thus, for these key patient characteristics, we could not
258 identify a clinically important subgroup who clearly benefit more from low-dose compared to
259 standard-dose alteplase. However, there was consistency in there being a lower risk of sICH for
260 low-dose alteplase across various age groups, between Asians and non-Asians, and for increasing
261 levels of neurological severity.

262 Our analyses provide the only randomized evidence comparing the effects of low-dose versus
263 standard-dose alteplase. Whilst sICH rates were lower with low-dose alteplase, this could not be
264 related to increasing age, and did not influence the differential treatment effect between the
265 alteplase doses on the disability outcomes. Thus, age is not a sufficient criterion to determine
266 which dose of alteplase to use; older AIS patients should not be systematically denied use of
267 standard-dose alteplase on the assumption that it is a more hazardous treatment in the very
268 elderly compared to those younger. Our randomized data partially contradict three observational
269 studies that have suggested that low-dose alteplase is associated with both a lower risk of sICH
270 and a higher odds of independent recovery for elderly AIS patients in eastern Asia.^{5,19,20}

271 As our results found no significant ethnic variation of the differential treatment effects of low-
272 dose versus standard-dose alteplase on the disability outcomes or for sICH, ethnicity cannot be

273 regarded as a modifying factor on the risks and benefits of low- versus standard-dose alteplase.
274 Systematic reviews^{21,22} that synthesize the current evidence of observational thrombolysis studies
275 in patients with AIS in Asia, are consistent with our findings in showing trends towards better
276 functional outcomes from standard compared to lower doses of alteplase, despite differential
277 risks of sICH. Despite the popular belief and underlying rationale for preferential use of low-
278 dose alteplase in Asian AIS patients because of higher bleeding risks from lytic treatment, our
279 pre-specified subgroup analysis of the ENCHANTED trial involving a large number and diverse
280 ethnic group of patients, did not indicate any variation in the differential treatment effects of the
281 two doses of alteplase between Asians and non-Asians. Thus, these findings do not support
282 current practice in many Asian countries to favor use of low-dose alteplase on the basis of it
283 being expected to be more efficacious than standard-dose alteplase.^{1,2,23}

284 The ENCHANTED trial was uniquely placed to assess the effects of low- versus standard-dose
285 alteplase by stroke severity, and to assess whether it modified the balance of benefits and risks.
286 Our analyses indicate that the benefits of low-dose alteplase in reducing sICH was not
287 significantly affected by stroke severity. Furthermore, the use of low-dose compared to
288 standard-dose alteplase was not associated with worse 90-day outcome, even in patients a severe
289 deficit. Although the benefits of standard-dose alteplase were independent of stroke severity, the
290 rate of favorable outcome depends on neurological severity.⁹ For patients with NIHSS ≥ 11 , the
291 absolute increases in good outcomes resulted from standard-dose alteplase versus placebo are
292 estimated at 3.2% to 4.5%. Thus, low-dose alteplase did not appear to alter the odds of recovery
293 in these types of patients.

294 Several strengths of our study are the large sample size, with a high proportion of older people
295 from both non-Asian and Asian populations in a variety of healthcare settings worldwide, which

296 enhance the generalizability of the results. Furthermore, there were high rates of patient follow-
297 up and adherence to treatment, and the rigorous assessment of serious adverse events especially
298 sICH, ensured that any harms associated with the treatments were reliably detected and
299 quantified. However, imprecision in the estimates of the treatment effect may have arisen from
300 inter-observer variability in mRS scoring,²⁴ and the inclusion of patients with generally mild
301 neurological severity treated with a longer delay from symptom onset than in other trials and
302 evaluations of alteplase in AIS⁹ may cause concern over the external validity of these results.
303 Finally, these are subgroup analyses with reduced statistical power that limited the ability to
304 detect modest differences between randomized group.

305 In conclusion, this pre-specified subgroup analyses of the ENCHANTED trial has shown that the
306 differential treatment effects of low-dose versus standard-dose alteplase on clinical outcomes
307 were consistent across subgroups defined by age, ethnicity, and severity of AIS. There was no
308 consistency in there being a lower risk of sICH with low-dose alteplate with increasing age,
309 between Asians and non-Asians, and with increasing neurological severity. Our results suggest
310 that decisions about the dose of alteplase used in thrombolysis-eligible AIS patients should not
311 be based solely on age, ethnicity, or stroke severity.

312

313 **Author contributions**

314 XW undertook the analyses and wrote the first and subsequent drafts of report; TR, RL, CSA,
315 and JC interpreted the data and wrote drafts of the report; TR, JK, RL, CSA and JC obtained
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349 **Additional contributors**

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352

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429 Table 1: Baseline characteristics by age group

	Age group (yr)					P value
	<50	50-59	60-69	70-79	≥80	
Time from stroke onset to randomization (hr)	2.7 (2.1-3.6)	2.8 (2.1-3.5)	2.8 (2.1-3.5)	2.7 (1.9-3.4)	2.5 (1.9-3.2)	<0.001
Female	115/ 352 (32.7)	196/ 626 (31.3)	289/ 897 (32.2)	397/ 950 (41.8)	251/ 472 (53.2)	<0.001
Ethnicity						<0.001
Non-Asian	98/ 352 (27.8)	163/ 624 (26.1)	273/ 895 (30.5)	334/ 948 (35.2)	344/ 472 (72.9)	
Asian	254/ 352 (72.2)	461/ 624 (73.9)	622/ 895 (69.5)	614/ 948 (64.8)	128/ 472 (27.1)	
Clinical features						
Systolic BP (mmHg)	143.1 (21.6)	147.4 (20.2)	150.3 (19.4)	150.1 (18.8)	152.8 (19.4)	<0.001
Diastolic BP (mmHg)	88.0 (13.5)	88.1 (12.2)	85.3 (12.1)	82.5 (12.8)	80.7 (13.4)	<0.001
Heart rate (beats per minute)	80.7 (12.9)	79.8 (14.5)	78.3 (14.5)	78.5 (16.8)	79.3 (16.7)	0.067
NIHSS score	8 (5 - 12)	7 (5 - 12)	8 (5 - 13)	9 (6 - 15)	10 (6 - 16)	<0.001
≥14	75/ 352 (21.3)	115/ 626 (18.4)	198/ 897 (22.1)	304/ 950 (32.0)	161/ 472 (34.1)	<0.001
GCS score	15 (14-15)	15 (14-15)	15 (14-15)	15 (13-15)	15 (13-15)	<0.001
Severe (3-8)	13/ 352 (3.7)	18/ 626 (2.9)	37/ 897 (4.1)	49/ 950 (5.2)	19/ 472 (4.0)	0.27
Medical History						
Hypertension	143/ 352 (40.6)	342/ 622 (55.0)	591/ 895 (66.0)	661/ 947 (69.8)	328/ 472 (69.5)	<0.001
Previous stroke	36/ 352 (10.2)	95/ 626 (15.2)	166/ 897 (18.5)	203/ 950 (21.4)	89/ 472 (18.9)	<0.001
Coronary artery disease	16/ 352 (4.6)	47/ 622 (7.6)	135/ 895 (15.1)	182/ 947 (19.2)	99/ 472 (21.0)	<0.001
Other heart disease (valvular or other)	19/ 352 (5.4)	31/ 622 (5.0)	61/ 895 (6.8)	69/ 947 (7.3)	55/ 472 (11.7)	0.004
Atrial fibrillation confirmed on ECG	23/ 352 (6.5)	60/ 622 (9.7)	136/ 894 (15.2)	253/ 946 (26.7)	164/ 471 (34.8)	<0.001
Diabetes mellitus	40/ 352 (11.4)	106/ 622 (17.0)	192/ 895 (21.5)	222/ 947 (23.4)	86/ 472 (18.2)	<0.001
Hypercholesterolemia	28/ 352 (8.0)	73/ 622 (11.7)	140/ 895 (15.6)	192/ 947 (20.3)	122/ 472 (25.9)	<0.001
Current smoker	119/ 352 (33.8)	205/ 621 (33.0)	252/ 895 (28.2)	163/ 945 (17.3)	31/ 471 (6.6)	<0.001
Pre-stroke function (mRS)						<0.001
No symptoms	328/ 352 (93.2)	554/ 622 (89.1)	744/ 894 (83.2)	759/ 946 (80.2)	289/ 472 (61.2)	
Symptoms without disability	24/ 352 (6.8)	68/ 622 (10.9)	150/ 894 (16.8)	187/ 946 (19.8)	183/ 472 (38.8)	
Medication at time of admission						
Antihypertensive agent(s)	71/ 352 (20.2)	208/ 622 (33.4)	411/ 895 (45.9)	516/ 947 (54.5)	292/ 472 (61.9)	<0.001
Warfarin anticoagulation	14/ 352 (4.0)	18/ 621 (2.9)	16/ 895 (1.8)	23/ 945 (2.4)	11/ 472 (2.3)	0.24
Aspirin or other antiplatelet agent	34/ 352 (9.7)	76/ 621 (12.2)	204/ 895 (22.8)	274/ 945 (29.0)	164/ 472 (34.8)	<0.001
Statin or other lipid lowering agent	33/ 352 (9.4)	73/ 621 (11.8)	155/ 895 (17.3)	223/ 944 (23.6)	131/ 472 (27.8)	<0.001
Brain imaging features						
Visible early ischemic changes	72/ 352 (20.5)	123/ 622 (19.8)	206/ 895 (23.0)	248/ 947 (26.2)	122/ 472 (25.9)	0.002
CT or MR angiogram shows proximal occlusion	45/ 350 (12.9)	88/ 618 (14.2)	129/ 886 (14.6)	171/ 936 (18.3)	72/ 456 (15.8)	0.069
Final diagnosis at time of hospital separation						
Non-stroke diagnosis	26/ 344 (7.6)	22/ 610 (3.6)	29/ 880 (3.3)	10/ 933 (1.1)	10/ 467 (2.1)	<0.001
Large artery occlusion due to significant atheroma	129/ 344 (37.5)	278/ 610 (45.6)	367/ 880 (41.7)	367/ 933 (39.3)	129/ 467 (27.6)	
Small vessel or perforating vessel lacunar disease	89/ 344 (25.9)	144/ 610 (23.6)	203/ 880 (23.1)	163/ 933 (17.5)	74/ 467 (15.9)	
Cardio-emboli	43/ 344 (12.5)	66/ 610 (10.8)	136/ 880 (15.5)	240/ 933 (25.7)	156/ 467 (33.4)	
Dissection	9/ 344 (2.6)	9/ 610 (1.5)	4/ 880 (0.5)	2/ 933 (0.2)	1/ 467 (0.2)	
Other or uncertain etiology	48/ 344 (14.0)	91/ 610 (14.9)	141/ 880 (16.0)	151/ 933 (16.2)	97/ 467 (20.8)	
Time from stroke onset to treatment (min)	175 (135-225)	176 (133-225)	175 (135-220)	170 (122-215)	153 (116-195)	<0.001
Treatment allocation to low-dose alteplase	179/ 352 (50.9)	312/ 626 (49.8)	441/ 897 (49.2)	478/ 950 (50.3)	244/ 472 (51.7)	0.92

430 Data are n (%), mean (SD), or median (IQR). The P values are based on Chi-square, ANOVA, or Kruskal Wallis test

431 BP indicates blood pressure, CT computerized tomography, ECG electrocardiogram, GCS Glasgow coma Scale, MRI magnetic

432 resonance imaging, mRS modified Rankin scale, NIHSS indicates National Institutes of Health Stroke Scale

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434

435 **Figure Legends**

436

437 **Figure 1 Randomized treatment effects on death or disability at 90 days by age, ethnicity,**
438 **and stroke severity**

439 Footnote: CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale.

440 ¹Data taken from Figure 2 of Anderson CS, Robinson T, Lindley RI, et al. Low-dose versus
441 standard-dose intravenous alteplase in acute ischemic stroke. *New Engl J Med* 2016; **374**: 2313–
442 23.

443 **Figure 2 Randomized treatment effects on symptomatic intracerebral hemorrhage by (A)**
444 **age, (B) ethnicity, and (C) stroke severity**

445 Footnote: CI: confidence interval; ECASS: European Co-operative Acute Stroke Study; IST:
446 International Stroke Trial; NIHSS: National Institutes of Health Stroke Scale; NINDS: National
447 Institute of Neurological Disorders and Stroke; OR: odds ratio; SITS-MOST: Safe
448 Implementation of Thrombolysis in Stroke Monitoring Study.

449 ¹The data shown in Panel B are taken from Figure S8 of Supplemental Appendix in Anderson
450 CS, Robinson T, Lindley RI, et al. Low-dose versus standard-dose intravenous alteplase in acute
451 ischemic stroke. *New Engl J Med* 2016; **374**: 2313–23.

452 **Figure 3 Randomized treatment effects on functional outcome according to the modified**
453 **Rankin scale at 90 days, by ethnicity**

454 Footnote: CI: confidence interval; mRS: modified Rankin scale; OR: odds ratio. Scores on the
455 mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant
456 disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe
457 disability, and 6 death.