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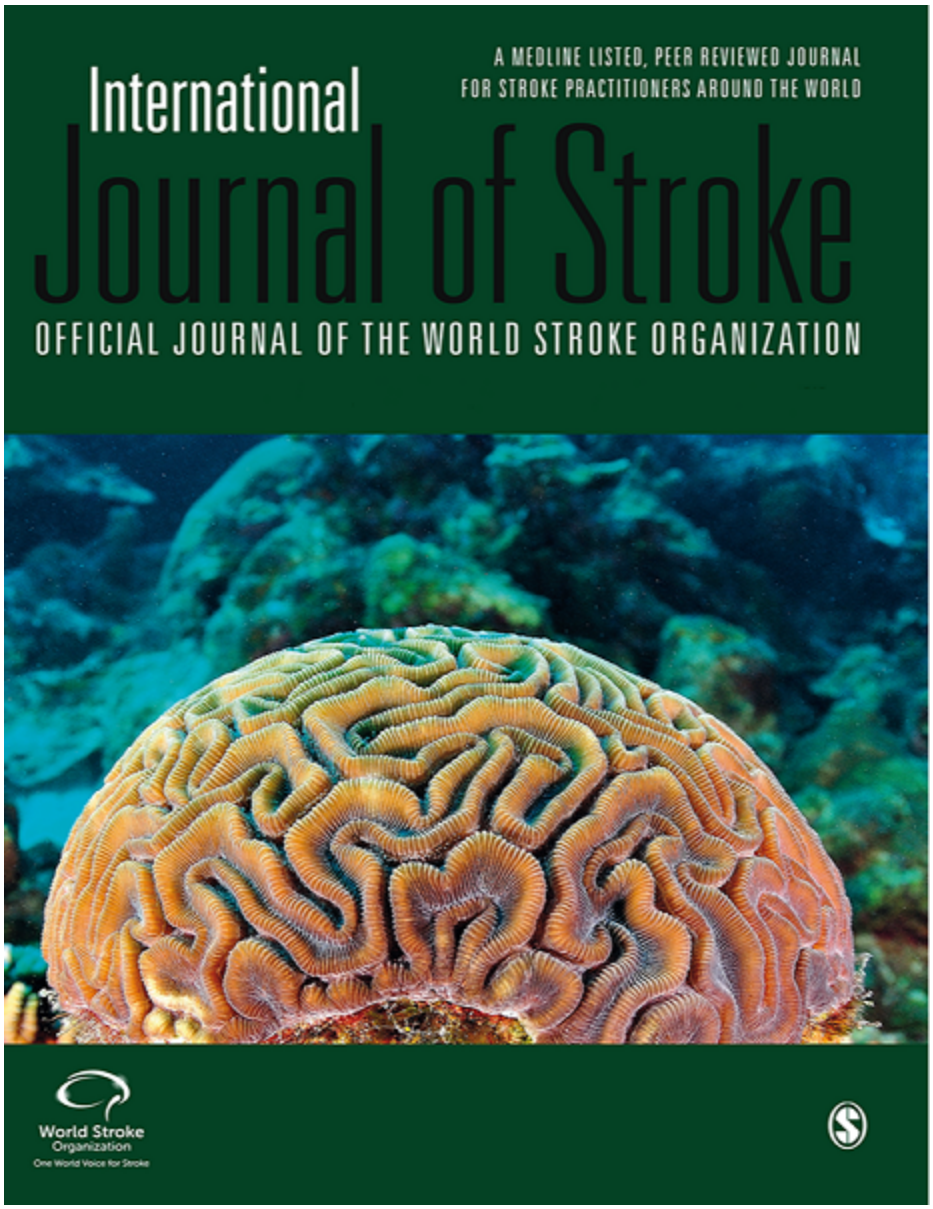

Low-dose versus standard-dose alteplase in acute ischaemic stroke in Asian stroke registries: an individual patient data pooling study

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Low-dose versus standard-dose alteplase in acute ischemic stroke in Asian stroke registries: an individual patient data pooling study

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For Review Only

Abstract

Objective: To investigate the comparative efficacy and safety of the low-dose versus standard-dose alteplase using real-world acute stroke registry data from Asian countries.

Methods: Individual participant data were obtained from 9 acute stroke registries from China, Japan, Philippines, Singapore, South Korea and Taiwan between 2005 and 2018. Inverse probability of treatment weight was used to remove baseline imbalances between those receiving low-dose vs standard-dose alteplase. The primary outcome was death or disability defined by modified Rankin Scale (mRS) scores of 2-6 at 90 days. Secondary outcomes were symptomatic intracerebral hemorrhage (sICH) and death. Generalized linear mixed models with the individual registry as a random intercept were performed to determine associations of treatment with low-dose alteplase and outcomes.

Results: Of the 6250 patients (mean age 66 years, 36% women) included in these analyses, 1610 (24%) were treated with low-dose iv alteplase. Clinical outcomes for low-dose alteplase were not significantly different to those for standard-dose alteplase, adjusted odds ratios for death or disability: 1.00 (0.85-1.19) and sICH 0.87 (0.63-1.19), except for lower death with borderline significance, 0.77 (0.59-1.01).

Conclusions: The present analyses of real-world Asian acute stroke registry data suggest that low-dose iv alteplase has overall comparable efficacy for functional recovery and greater potential safety in terms of reduced mortality, to standard-dose alteplase for the treatment of acute ischemic stroke.

Key words- acute ischemic stroke; thrombolysis; alteplase dose; symptomatic intracranial hemorrhage; individual patient analysis; Asian

For Review Only

Introduction

Recombinant tissue plasminogen activator (rtPA/alteplase) is the established treatment for acute ischemic stroke (AIS). Most guidelines[1, 2] recommend an intravenous (iv) dose of 0.9 mg/kg of alteplase (10% as a bolus and the remaining as an infusion over 1-hour; maximum dose 90mg) to eligible patients with AIS, presenting within 3 or 4.5 hours of symptom-onset, based on the National Institute of Neurological Disorders and Stroke (NINDS)[3] and the European Cooperative Acute Stroke Study (ECASS) trials,[4-6] respectively. However, a dose of 0.6 mg/kg (10% as a bolus and the remaining as an infusion over 1 hour; maximum dose 60mg) is the approved dose of alteplase in Japan[7], where non-randomized studies[8-11] have suggested comparable clinical outcomes and reduced risk of symptomatic intracerebral hemorrhage (sICH) compared to the standard-dose.[8, 9] In other Asian countries, low-dose alteplase is used widely, largely due to the reduced cost and anticipated lower rates of sICH.[12, 13]

The ENhanced Control of Hypertension And Thrombolysis strokE stuDy (ENCHANTED)[13-15] has been the only randomized comparison of low- versus standard-dose iv alteplase in AIS patients who fulfilled standard eligibility criteria for this treatment. The study demonstrated that low-dose alteplase did not meet the stringent non-inferiority criteria compared to standard-dose alteplase with respect to the conventional binary clinical endpoint of death and disability, defined by scores of 2-6 on the modified Rankin scale (mRS) at 90 days. However, low-dose alteplase was non-inferior with respect to an ordinal analysis of this endpoint, and there were significantly fewer cases of sICH across all standard criteria in the low-dose alteplase group. The ENCHANTED results have stimulated debate about the widespread use of low-dose alteplase in Asian medical practice.

Systematic reviews[16, 17] comparing low- and standard-dose alteplase have shown little difference in clinical outcomes, possibly due to individual studies being under-powered.

For Review Only

Hence, we initiated an international collaborative, individual patient data (IPD) pooling project, to compare low- and standard-dose alteplase, with the aim of providing reliable evidence about the optimal dose of iv alteplase for Asian AIS patients.

METHODS

This study was based on IPD and adhered to the PRISMA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data).[18] All participating studies were approved by their local ethics committees. Data were obtained from 9 stroke registries from 6 Asian countries (China, Japan, Philippines, Singapore, South Korea and Taiwan), 6 of which were identified by a systematic search, representing 50% of the 12 potentially eligible studies with sample size over 100;[19] 3 were unpublished. We requested de-identified IPD on patient characteristics, the dose of alteplase and outcomes from the study investigators. The reasons for excluding 6 studies were ethical approval not being granted (4) and refusal to participate (2) (Supplementary table 1).

We collected information on factors that might explain the differences in the association between alteplase-dose treatment and outcomes including: (i) alteplase treatment (time from onset to treatment and dosage); (ii) demographics (age, sex, body weight, country of recruitment); (iii) medical history (hypertension, previous stroke, coronary artery disease, atrial fibrillation, diabetes, hypercholesterolemia and smoking); (iv) medication history (antihypertensive medication, lipid-lowering medication, antidiabetic medication, warfarin use, aspirin or other antiplatelet use); (v) hemodynamic parameters (systolic/diastolic blood pressure, heart rate); and (vi) stroke severity (the National Institute of Health Stroke Scale [NIHSS]) and stroke etiology according to the Trial of Org 10172 in acute stroke treatment (TOAST) classification[20].

For Review Only

Functional outcome was measured by mRS at 3 months. The definition of sICH varied among the studies: 3 studies defined it as per the NINDS trial[3], 5 studies defined it as radiological evidence of ICH associated with neurological deterioration (4 used a corresponding 4-points increase on the NIHSS; 1 study used a 2-point increase), and 1 study defined it as per the ECASS II[5] trial (any ICH with neurological deterioration [>4 points on the NIHSS) from baseline or death within 24 to 36 hours) (Supplementary table 2).

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Statistical analysis

Initial internal analyses were performed to compare baseline and outcome data from each study with their published results to ensure that data were complete and transferred without error. Since most of the individual study results have already been published, results from analysis of individual studies will not be identifiable in this publication. We, therefore, used the 1-stage method of analysis proposed for IPD meta-analyses.

The characteristics of the low-dose alteplase group were expected to substantially differ from those of the standard-dose group. To generate a comparable data set, we calculated a propensity score to estimate the individual probability of a patient receiving low-dose alteplase. Six variables were used as covariates to calculate propensity scores (sex, age, baseline systolic blood pressure [SBP], baseline NIHSS, premorbid mRS, time from onset to treatment, and presence of vascular risk factors [prior transient ischemic stroke, stroke, hypertension, coronary artery disease, atrial fibrillation, diabetes or hypercholesterolemia]). The inverse probability of treatment weighting (IPTW) was used as the primary strategy to adjust for baseline imbalances.[21] Data balancing was examined using an absolute standardized difference in covariate means.[22] The distributions of baseline covariates were

For Review Only

fairly well balanced by applying propensity scores; the absolute standardized differences after IPTW were within an acceptable margin of 0.1 (supplementary figure 1). Stabilized weights[23] were used to reduce variance of the estimated effect of low-dose alteplase, and were incorporated into generalized linear mixed models with the individual registry as a random intercept to determine associations of treatment with low/standard-dose alteplase and outcomes.

For all analyses involving the primary outcome of functional recovery (ordinal scores on the mRS), we checked the proportional odds assumption was not violated; where this was violated, we present functional outcome according to binary mRS scores. Subgroup analyses by key demographic variables (sex; age <65 vs. ≥65 years), clinical severity (defined by NIHSS scores <10 vs. ≥10 points), treatment (time from onset to treatment <3 vs. ≥3 hours), TOAST classification (large-artery atherosclerosis, small-vessel, cardioembolism, and other etiology) and premorbid mRS (0-1 vs. 2-5)were undertaken to test the consistency of any association. We assessed the heterogeneity of association in subgroups by adding an interaction term in the models. Data are presented as odds ratios (OR) and 95% confidence intervals (CI). A two sided P <0.05 was set as the level for statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS institute, Cary, NC, USA).

Results

There were 6852 patients from 8 studies, 6250 of which were treated either by low-dose alteplase (0.55-0.65 mg/kg, 23.4%) or standard-dose alteplase (0.85-0.95 mg/kg, 66.6%). Data for sICH were available in all patients, mRS data in 4055, and sICH data in 6250 patients. The mean age of the patients was 66 years, 37% were female, and the median NIHSS was 10 (IQR 6-16). Table 1 shows the baseline characteristics of patients according to alteplase dosage: those in the low-dose group were significantly older and more neurologically impaired, and a higher proportion were female, hypertensive, and with co-

For Review Only

morbidity. Additionally, strokes due to large-artery atherosclerosis were more likely to be treated with standard-dose alteplase, while strokes due to cardioembolism were more likely to be treated with low-dose alteplase.

The distribution of mRS scores at 3 months was shown in figure 1. Compared to standard-dose alteplase, treatment with low-dose alteplase was not associated with death and disability (mRS 2-6) at 3 months (OR 1.00, CI 0.85-1.19) or sICH (OR 0.87, CI 0.63-1.19) (Figure 2). However, treatment with low-dose alteplase was associated with lower risk of 3-month mortality with borderline significance (OR 0.77, CI 0.59-1.01).

Figure 3 shows that associations were consistent across the key subgroups by age, sex, stroke severity,time from onset to treatment, and stroke subtype. Although, significant heterogeneity was evident for dichomtised premorbid mRS (0-1 vs. 2-5), the current study is under-powered to explore the association for the subgroup of premorbid mRS 2-5.

DISCUSSION

This IPD meta-analysis aimed to provide reliable evidence about the efficacy and safety of low-dose alteplase in real world Asian populations, adjusted for important confounders. Our analyses of pooled data from 9 real-world acute stroke registries from Asian countries show that low-dose alteplase treatment of AIS has comparable overall efficacy and potentially improved safety compared with standard-dose alteplase when used to treat AIS within 4.5 hours of onset.

We confirm findings from previous comprehensive systematic reviews that show low- and standard-dose alteplase have equivalent outcomes for the treatment of AIS.[12, 19] In the present study, 63% of patients who were treated with low-dose alteplase had the outcome of death or disability (mRS 2-6), which is similar to the single-arm nonrandomized studies first and second Japan Alteplase Clinical Trial (J-ACT 1 and 2), and the Japan Post-marketing

For Review Only

Alteplase Registration Study (JMARS). Additionally, 55% of patients treated with standard-dose alteplase had the outcome of death or disability, which is comparable to data from the multinational Safe Implementation of Thrombolysis in Stroke–Non-European Union World study,[24] NINDS trial,[3] and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).[25] These similarities support the reliability of our large dataset of pooled real-world IPD.

In regard to functional outcome at 90 days, we found that for those treated with low-dose alteplase, a smaller proportion of deaths was accompanied by an increase in moderate to severe disability amongst survivors – a finding that is consistent with that of the ENCHANTED trial. This finding occurred despite differences in patient characteristics at baseline; patients enrolled in ENCHANTED were younger, had milder deficits, were treated with alteplase at a longer time from the onset of symptoms, and were less likely to have atrial fibrillation or major arterial occlusion. These factors may be considered barriers to implementation of the ENCHANTED findings directly into clinical practice, however our real-world data provide support for the generalizability of these trial results.

A notable point of difference relates to alteplase dose and sICH risk; the ENCHANTED trial showed that low-dose alteplase significantly reduced the risk of sICH, however our analyses showed no such association. This discordance could be explained by differences between the definitions used to identify sICH in a clinical trial and across real-world clinical practice in several different healthcare systems; it may also be explained by inadequate adjustment for confounders. For example, we did not have information on prior antiplatelet or anticoagulant use, both of which are important prognostic factors in thrombolysis-associated ICH. Another limitation of the present study is data availability bias arising from our inability to acquire IPD from 4 large registries in Japan and Taiwan (8840 patients) due to ethical approval issues. In addition, there is significant difference in time from onset to treatment and

For Review Only

countries contributing standard and low-dose alteplase patients which may have affected our overall results. However higher age, higher NIHSS are points against for low-dose alteplase, which may have nullified effects though we have conducted propensity score matching analysis.

Prior to this work, observational studies from Asia reported conflicting findings. For instance, low-dose alteplase was found to be equivalent to standard-dose in a large observational registry from South Korea.[26] Conversely, the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke registry in China showed that standard-dose alteplase produced favorable outcomes without increasing the risk of sICH.[27] Therefore, our analyses of pooled IPD, which include the aforementioned studies, provide clarity in producing a comprehensive summary of the evidence, and greater power to detect meaningful associations between alteplase dose and outcome, adjusted for important confounders.

In summary, this international collaborative project, curated and analyzed IPD from a wide variety of Asian stroke registry studies, reports that low- and standard-dose alteplase have equivalent outcomes in AIS. This finding needs to confirmed in a randomised clinical trial including patients undergoing mechanical thrombectomy as well.

For Review Only

References

1. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2016;47:581-641.
2. Royal College of Physicians. Stroke guidelines. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines (accessed November 24, 2016).
3. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. The New England Journal of Medicine 1995;333:1581-1587.
4. Hacke W, Kaste M, Fieschi C, 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.
5. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251.
6. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England Journal of Medicine 2008;359:1317-1329.
7. Minematsu K, Toyoda K, Hirano T, et al. Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase), the second edition, October 2012: a guideline from the Japan Stroke Society. Journal of stroke and cerebrovascular diseases 2013;22:571-600.
8. Yamaguchi T, Mori E, Minematsu K, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37:1810-1815.
9. Mori E, Minematsu K, Nakagawara J, et al. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). Stroke 2010;41:461-465.
10. Nakagawara J, Minematsu K, Okada Y, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41:1984-1989.
11. Toyoda K, Koga M, Naganuma M, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591-3595.
12. Sharma VK, Ng KW, Venketasubramanian N, et al. Current status of intravenous thrombolysis for acute ischemic stroke in Asia. Int J Stroke 2011;6:523-530.
13. Huang Y, Sharma VK, Robinson T, et al. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2 x 2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischemic stroke eligible for thrombolysis treatment. Int J Stroke 2015;10:778-788.
14. Anderson CS, Robinson T, Lindley RI, et al. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. The New England Journal of Medicine 2016;374:2313-2323.

For Review Only

15. Anderson CS, Woodward M, Arima H, et al. Statistical analysis plan for evaluating low- vs. standard-dose alteplase in the ENhanced Control of Hypertension and Thrombolysis strokE stuDy (ENCHANTED). Int J Stroke 2015;10:1313-1315.
16. Liu MD, Ning WD, Wang RC, et al. Low-Dose Versus Standard-Dose Tissue Plasminogen Activator in Acute Ischemic Stroke in Asian Populations: A Meta-Analysis. Medicine 2015;94:e2412.
17. Sharma VK, Ng KWP, Venketasubramanian N, et al. Current status of intravenous thrombolysis for acute ischemic stroke in Asia. Int J Stroke 2011;6:523-530.
18. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657-1665.
19. Wang X, You S, Sato S, et al. Current status of intravenous tissue plasminogen activator dosage for acute ischemic stroke: an updated systematic review. Stroke Vasc Neurol 2018;3:28-33.
20. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
21. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-560.
22. Haviland A, Nagin DS, Rosenbaum PR. Combining propensity score matching and group-based trajectory analysis in an observational study. Psychol Methods 2007;12:247-267.
23. Rheta E. Lanehart PRdG, Eun Sook Kim, Aarti P. Bellara, Jeffrey D., Kromrey aRSL. Propensity score analysis and assessment of propensity score approaches using SAS procedures [online]. Available at: http://support.sas.com/resources/papers/proceedings12/314-2012.pdf.
24. Rha JH, Shrivastava VP, Wang Y, et al. Thrombolysis for acute ischemic stroke with alteplase in an Asian population: results of the multicenter, multinational Safe Implementation of Thrombolysis in Stroke-Non-European Union World (SITS-NEW). International Journal of Stroke 2014;9 Suppl A100:93-101.
25. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-282.
26. Kim BJ, Han MK, Park TH, et al. Low-Versus Standard-Dose Alteplase for Ischemic Strokes Within 4.5 Hours: A Comparative Effectiveness and Safety Study. Stroke 2015;46:2541-2548.
27. Liao X, Wang Y, Pan Y, et al. Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. Stroke 2014;45:2354-2358.
28. Chao AC, Hsu HY, Chung CP, et al. Outcomes of thrombolytic therapy for acute ischemic stroke in Chinese patients: the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study. Stroke 2010;41:885-890.
29. Nguyen TH, Truong AL, Ngo MB, et al. Patients with thrombolysed stroke in Vietnam have an excellent outcome: results from the Vietnam Thrombolysis Registry. Eur J Neurol 2010;17:1188-1192.
30. Zhou XY, Wang SS, Collins ML, Davis SM, Yan B. Efficacy and safety of different doses of intravenous tissue plasminogen activator in Chinese patients with ischemic stroke. Journal of Clinical Neuroscience 2010;17:988-992.
31. Chen CH, Hsieh CY, Lai TB, Chuang MT, Chen WL, Sun MC. Optimal dose for stroke thrombolysis in Asians: Low dose may have similar safety and efficacy as standard dose. Journal of Thrombosis and Haemostasis 2012;10:1270-1275.

For Review Only

32. Chao AC, Liu CK, Chen CH, et al. Different doses of recombinant tissue-type plasminogen activator for acute stroke in Chinese patients. Stroke 2014;45:2359-2365.

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Figure legends

Figure 1: mRS distribution by low-dose versus standard-dose alteplase

Figure 2: Association between low-dose and standard-dose alteplase and clinical outcomes

Model a: propensity score was derived from the model with sex, age, baseline NIHSS, time from onset to treatment, and risk factor (prior TIA, stroke, hypertension, coronary artery disease, AF, diabetes, or hypercholesterolemia]

Model b: propensity score was derived from the model with sex, age, baseline NIHSS score, premorbid modified Rankin Scale(mRS), time from onset to treatment, and risk factor (prior TIA, stroke, hypertension, coronary artery disease, AF, diabetes, or hypercholesterolemia]

Figure 3 subgroup analysis

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Table 1. Baseline characteristics

	Standard-dose alteplase (0.9 mg/kg) (n=4640)	Low-dose alteplase (0.6 mg/kg) (n=1610)	P value
Age, mean (SD)	65.1(12.0)	68.4(12.9)	<0.0001
Female	1640/4598(35.7)	604/1548(39.0)	0.018
Time from stroke onset to treatment, median(IQR)	2.52(1.83-3.08)	2.30(1.75-2.83)	<0.0001
Country			<0.0001
China	2877/4640(62.0)	347/1610(21.6)	
Korea	1076/4640(23.2)	450/1610(28.0)	
Japan	0(0.00)	600/1610(37.3)	
Taiwan	368/4640(7.9)	22/1610(1.4)	
Singapore	224/4640(4.8)	135/1610(8.4)	
Philippines	95/4640(2.1)	56/1610(3.5)	
NIHSS, median(IQR)	9(5-15)	11(6-18)	<0.0001
SBP	148.6(24.9)	151.1(23.6)	0.0002
DBP	86.2(14.9)	84.3(16.0)	<0.0001
Pre-morbid mRS			<0.0001
0-1	2610/4117(63.4)	1100/1413(77.9)	
2-5	1507/4117(36.6)	313/1413(22.2)	
Smoking	1662/4512(36.8)	368/1007(36.5)	0.863
Prior stroke	657/3545(18.5)	237/1149(20.6)	0.116
Prior coronary artery disease	104/2281(4.6)	160/944(17.0)	<0.0001
Prior atrial fibrillation	1097/4640(23.6)	606/1600(37.9)	<0.0001
Prior hypertension	2961/4640(63.8)	1068/1606(66.5)	0.053
Prior dislipidemia	853/4638(18.4)	438/1603(27.3)	<0.0001
Prior diabetes mellitus	1046/4640(22.5)	383/1609(23.8)	0.300
TOAST classification			<0.0001
Large-artery atherosclerosis	854/2287(37.3)	369/1475(25.0)	
Small-vessel occlusion	243/2287(10.6)	143/1475(9.7)	
Cardioembolism	678/2287(29.7)	694/1475(47.1)	
Others	512/2287(22.4)	269/1475(18.2)	

SD: standard deviation; IQR: interquartile range; mRS: modified Rankin Scale; TOAST: Aetiological Trial of Org 10172 in acute stroke treatment (TOAST) classification

For Review Only

[redacted]

Figure 1

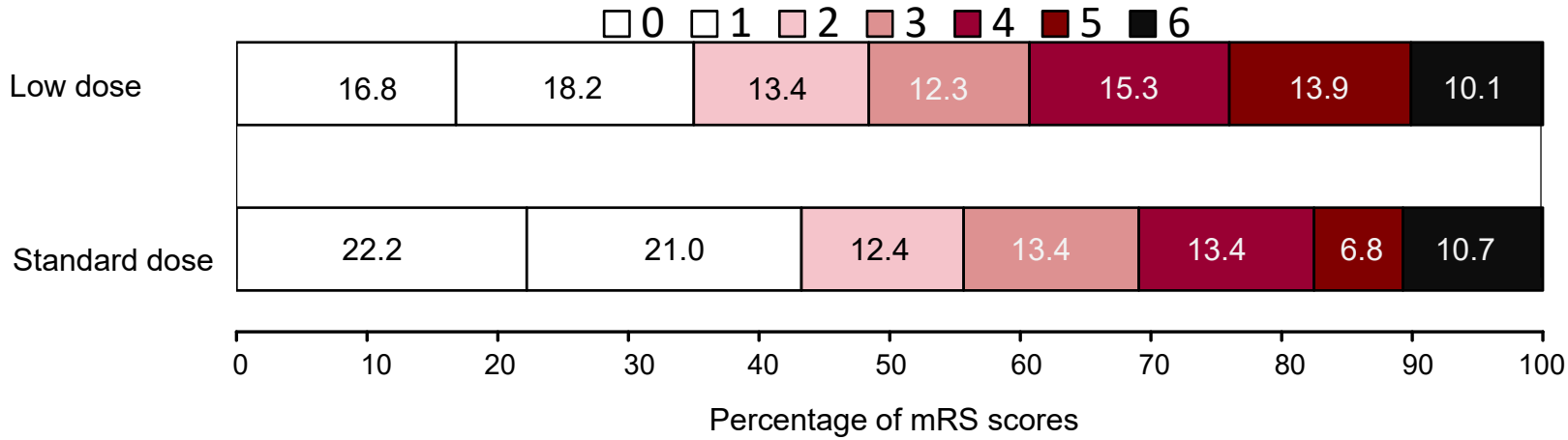

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Figure 2

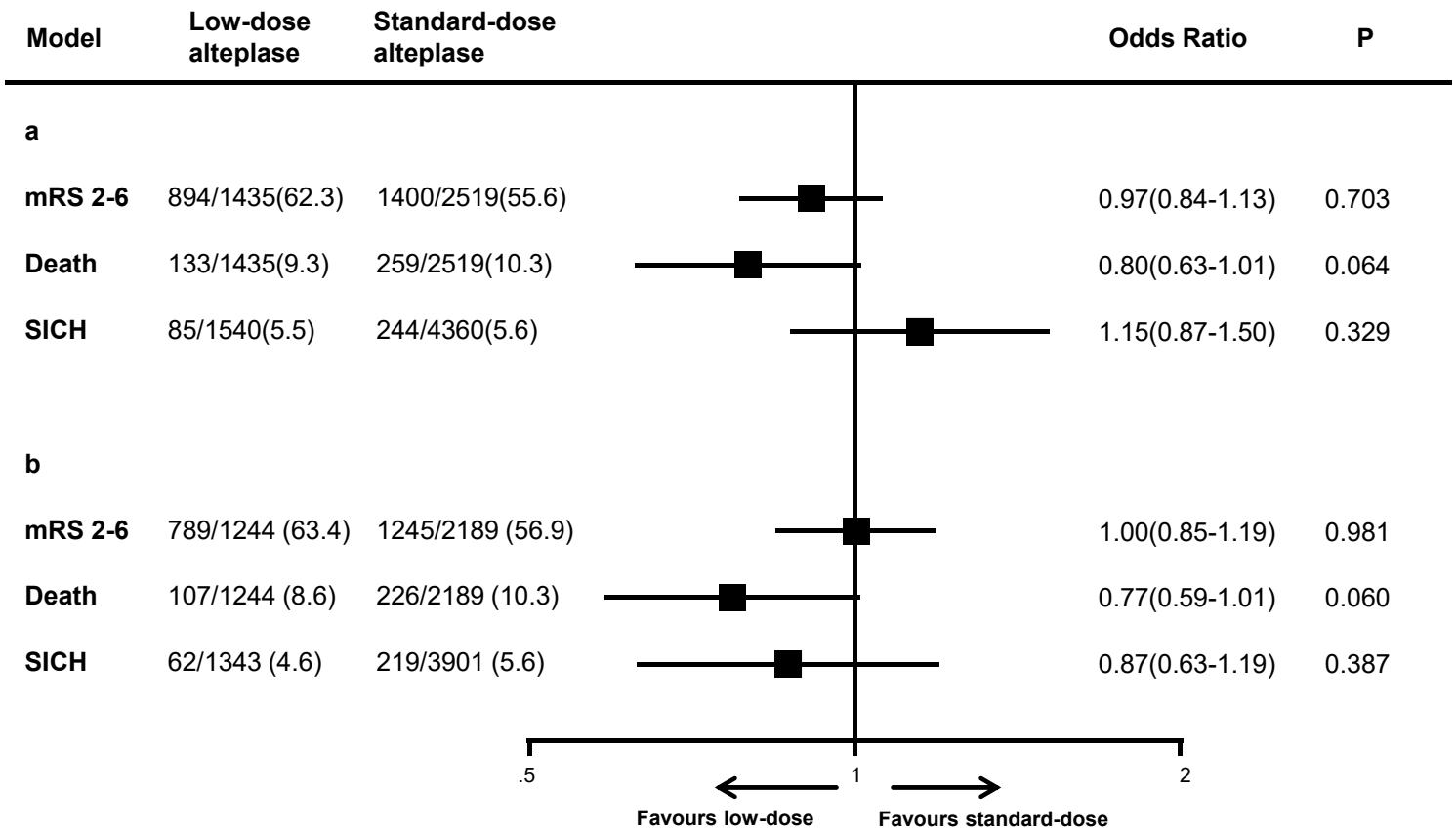

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Figure 3