Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Table of Contents

No	Title	Page
1	List of ENCHANTED study group and trial investigators	4
2	Agencies providing funding for the study	9
3	Screening procedures	9
4	Inclusion/exclusion criteria	9
5	Training of investigators	10
6	Schedule of monitoring of sites	10
7	Definitions of protocol violations and deviations	11
8	Complete list of major and minor protocol violations	12
9	Sample size calculations	24
10	Terms of reference of the Data Safety Monitoring Board (DSMB)	24
11	Procedures and criteria used for the assessment of intracranial hemorrhage	26
12	Protocol violations in use of alteplase	28
13	Assessments of functional outcome and health-related quality of life	28
14	Tables	30
	1. Reasons that patients with acute ischemic stroke were excluded from participating in the trial	31
	2. Characteristics of the patients at baseline and process measures in the per-protocol on treatment analysis set	32
	3. (a) Dosing of alteplase to participants (b) Dosing of alteplase to participants, by major ethnic group	34
	4. Non-compliance with trial treatment protocol	35
	5. Management details from randomisation to Day 7	36
	6. Source of information on outcome assessments	38
	7. Mean (SD) systolic blood pressure readings by alteplase dose treatment group	39
	8. Post-hoc assessment of the primary outcome according to the simplified modified Rankin scale questionnaire (smRSq)	40
	9. Distribution of categories on the modified Rankin scale (mRS) between low dose and standard dose alteplase using the assumption-free statistical method of Howard	42
	10. Other secondary outcomes at 3 months	43
	11. Causes of death during follow-up to 3 months	45
	12. Serious adverse events (SAEs) to the close of study	46
14	Figures	48
	1. Eligibility, randomization and follow-up of patients	49

	2. Distribution of dose of alteplase based on measured body weight, by randomized group	50
	3. Comparative effects on the primary outcome by different analytical approaches	51
	4. Post-hoc comparative effects on the primary outcome using the simplified modified Rankin scale questionnaire, by different analytical approaches	52
	5. Comparative effects on the primary outcome by time (<3 vs. ≥3 hours) from stroke onset to start of alteplase	53
	6. Effects of low dose alteplase compared to standard dose alteplase on functional outcome according to an adjusted ordinal analysis of all categories of the modified Rankin scale (mRS) at 90 days, according to predefined covariates	54
	7. Effects of low-dose alteplase compared to standard-dose alteplase on different classifications of intracerebral hemorrhage	55
	8. Effects of low dose alteplase compared to standard dose alteplase on symptomatic intracerebral haemorrhage (ICH) by different criteria during 90 days of follow-up, in Asians versus non-Asians	56
	9. Cumulative mortality curves for death by dose of alteplase	57
	10. Effects of low dose alteplase compared to standard dose alteplase according to ordinal analysis of functional outcome on the modified Rankin scale at 90 days, according to predefined subgroups	58
	11. Effects of low dose alteplase compared to standard dose alteplase on death during 90 days of follow-up, according to predefined subgroups	59
	12. Relation of treatment effect by baseline National Institutes of Health Stroke Scale (NIHSS) score	60

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2. Agencies providing funding for the study

The National Health and Medical Research Council (NHMRC) of Australia, the Stroke Association of the United Kingdom, the National Council for Scientific and Technological Development of Brazil, and the Ministry for Health, Welfare and Family Affairs of the Republic of Korea. These agencies had no role in the design of the trial protocol, in the collection, analysis, or interpretation of the trial data, or in the writing of the manuscript.

3. Screening procedures

Study personnel were required to maintain screening logs of all patients who present with acute ischemic stroke during the study period. However, screening logs were prohibited for sites in the United Kingdom where prospective minimum data are collected as part of the Sentinel Stroke National Audit Program (SSNAP). At the end of the study period, the SSNAP data submitted from each participating site during their period of activation in the study were interrogated to assess the participation of patients with acute ischemic stroke in ENCHANTED. For all other participating sites outside of the United Kingdom, data were used from screening logs submitted to the International Coordinating Center each month during participation in the study.

4. Inclusion/exclusion criteria

Patient specific inclusion criteria: All patients were eligible if they fulfilled general eligibility criteria for thrombolytic treatment with intravenous alteplase as well as the following specific criteria:

- men or women aged ≥18 years with a clinical diagnosis of acute ischemic stroke confirmed by brain imaging;
- able to receive thrombolysis treatment within 4.5 hours of symptom onset;
- were previously independent, as defined by a prestroke functional ability of 1 or less on the modified Rankin scale (mRS);
- systolic blood pressure ≤185 mmHg (the guideline recommended level for use of alteplase; patients with higher BP can still be included provided the BP is reduced to the entry level prior to commencement of alteplase); and
- no definite indication nor contraindication for either dose of alteplase

Exclusion criteria: Potential patients who met any of the following criteria were excluded from participating in the study:

- unlikely to benefit from the therapy due to pre-existing disability (e.g. advanced dementia) or very high likelihood of death within 24 hours;
- another medical illness that interferes with outcome assessments;
- unlikely to adhere to follow-up procedures;
- no consent to participate;
- previously enrolled in ENCHANTED.

5. Training of investigators

All ENCHANTED investigators were trained in the protocol, Good Clinical Practice (GCP) and use of the NIHSS and mRS scales if they had no recent certification.

6. Schedule for monitoring of sites

Regionally based research staff undertook quality control activities necessary for the conduct of the trial in accordance with the protocols, applicable guidelines and regulations. The first monitoring visit following initiation and activation of the site took place after the site had randomised 3 patients. The second monitoring visit took place after every 10–20 patients had been randomised. Subsequent monitoring visits took place after every 20–50 patients had been randomized after the previous visit, although the interval for monitoring visits was longer or shorter according to patient enrolment rate, quality issues, trial site compliance, or other trial site issues. All sites were monitored at least every 12 months. Any significant deviation from the planned monitoring timelines was explained and documented in the monitoring visit report, and the monitoring plan was amended if appropriate.

The monitoring visit served to obtain 100% source data verification of the following data for all patients randomized: patient consent forms (patient consent forms were reviewed for compliance with ICH GCP); patient existence; diagnosis of ischemic stroke; all outcome data; treatment allocation; and all serious adverse event forms to source verification.

For 10% of randomly selected randomized patients, or patients identified by the International Coordinating Center (ICC) or Regional Coordinating Center (RCC), all data entered in the electronic case record form (eCRF) were verified against source data.

Differences in the monitoring schedule to that outlined above occurred in certain countries: (i) Korea – had all data source verified for the first patient at every site, and all data source was verified in 20% of randomly selected patients; and (ii) Brazil – because of the limited time available to close out the alteplase dose arm of the trial, most of the randomized patients only had 100% source verification of consent, existence, diagnosis of ischemic stroke, and outcome data, but without further selection of 10% patients for verification of source data.

At the end of the study, 97 sites had received at least one interim monitoring visit and the median number of monitoring visits amongst these sites was 3. A total of 330 monitoring visits were conducted: 76% sites were visited 1 to 5 times, and 14% were visited between 6 and 11 times.

7. Definitions of protocol violations and deviations

Protocol deviation / violations are any unapproved changes, or departures from the study design or procedures of the ENCHANTED protocol that are under the investigator's control and that have not been reviewed and approved by the ICC, IRB/EC. Protocol Deviation / Violations are divided into two categories: 'major (reportable) violations' and 'minor (non-reportable) violations' which are also called 'Protocol Deviations'.

Major (reportable) protocol violations

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the ENCHANTED approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. All major violations are required to be reported to the ethics board, regulatory authority and/or sponsor in keeping with relevant national guidance, and conforming to national timelines for reporting. The ICC criteria for defining major violations include any of the following.

- The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
- The violation resulted in a change to the participant's clinical or emotional condition or status.
- The violation has damaged the scientific completeness or soundness of the data collected for the study.
- The violation is evidence of wilful or knowing misconduct on the part of the investigator(s).
- The violation involves serious or continuing noncompliance with federal, state or local regulations.

Examples of major protocol violations include, but are not limited to:

a) enrolment of participants who did not meet the eligibility requirements;

b) failure to obtain informed consent prior to any study-specific tests/procedures

c) failure to follow protocol procedures that specifically relate to the primary safety or efficacy endpoints of the study.

Minor (non-reportable) protocol violations (also called protocol deviations)

Minor protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the ENCHANTED approved protocol that do not have a major impact on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Minor protocol violations are not necessarily reportable to the IRB/EC. ICC criteria for minor violations include all of the following:

- the violation did not harm or pose a significant risk of substantive harm to the research participant, and

- the violation did not result in a change to the participant's clinical or emotional condition or status, and
- the violation did not damage the completeness, accuracy and reliability of the data collected for the study, and
- the violation did not result from wilful or knowing misconduct on the part of the investigator(s), and
- the violation did not involve serious or continuing noncompliance with federal, state or local regulations.

Examples of minor protocol violations include, but are not limited to:

1) Routine safety lab work for a participant without new clinical concerns and a history of previously normal lab values is inadvertently omitted at a study visit or performed outside the protocol-defined window.

2) Patient unable to complete self-administered quality of life questionnaire when they are capable to do it.

3) Follow up visits / assessments are performed outside of protocol defined time points or time window.

8. Complete list of major and minor protocol violations

These are listed in the following pages.

Protocol violation summary for alteplase patients in Part A (alteplase dose arm) of ENCHANTED study

Major/Minor	Discription 1	Discription 2	Code	Australia	Brazil	Chile	China	Colombia	Italy	Korea	Singapore	Taiwan	UK	Vietnam	Total
MAJOR	Local SAE/s reported to EC (MHRA and REC in UK)	Not reported within timeframe	219			1	14	2		2			1	6	26
minor	Baseline brain imaging taken date & time	Not collected/ recorded	303				1								1
minor	Heart rate prior to randomisation	Not collected/ recorded pre-randomisation	307										1		1
MAJOR	Body weight for alteplase dose calculation	Not collected/ recorded pre-randomisation	308										1		1
minor	GCS score prior to randomisation	Not collected/ recorded pre-randomisation	309							4					4
MAJOR	NIHSS score prior to randomisation	Not collected/ recorded pre-randomisation	310										1		1
MAJOR	Acute ischaemic stroke, confirmed by brain imaging (CT or MRI)	Acute ischaemic stroke not confirmed by brain imaging(CT or MRI) ;	312							2					2
MAJOR	Acute ischaemic stroke, confirmed by brain imaging (CT or MRI)	Acute ischaemic stroke confirmed by brain imaging(CT or MRI) after randomisation but not pre-randomisation.	313											3	3
MAJOR	Able to receive alteplase treatment	Commence alteplase treatment >4.5 hours from onset	315	1			6						9	2	18
MAJOR	Known definite contraindication for alteplase	Patient has contraindication to alteplase	316							27					27
MAJOR	Unlikely to benefit from the therapy (eg advanced dementia)	Patient unlikely benefit from the treatment	317				1								1

MAJOR	Other medical conditions that interfere with outcome assessments (eg advanced cancer, renal failure or known significant pre-stroke disability [mRS of 2-5])	Patient has other medical conditions that interfere with outcome assessments	319			1	1			2			10		14
MAJOR	Previous participation in this trial or current participation in an investigational drug trial	Previous participation in this trial	320				1								1
MAJOR	A high likelihood that the patient will not be able to be followed up (eg visiting city from rural location)	Likelihood patient will not be able to be followed up	322										1		1
MAJOR	Able to receive either low-dose or standard-dose alteplase	Patient has indication or contraindication to low-dose or standard-dose alteplase	323				1								1
MAJOR	Appropriate consent for PART [A] THROMBOLYSIS DOSE	No appropriate consent for PART [A] THROMBOLYSIS DOSE but patient was randomized into PART [A].	324				3						2		5
MAJOR	Will be receiving some form of iv alteplase, irrespective of whether or not is being randomised in PART [A]	No i.v. alteplase is received.	325		1		12			8			10	4	35
MAJOR	Systolic BP ≥ 150	Both BP readings < 150 mmHg prior to randomisation;	326				1								1
minor	Systolic BP ≥ 150	Only one BP reading ≥ 150 prior to randomisation	327				1			1					2
MAJOR	Able to receive either intensive BP lowering or conservative BP management	Patient has indication or contraindication to either BP lowering regimen.	328							1					1
MAJOR	Appropriate consent for PART [B] BP LOWERING THERAPY	No appropriate consent for PART [B] BP LOWERING THERAPY but patient was randomized into PART [B].	329	1			2								3
minor	Acute ischaemic stroke, confirmed by brain imaging (CT or MRI)	Non-ischaemic stroke confirmed after randomisation, even though patient is diagnosed ischaemic stroke before randomisation;	330										3		3
minor	Initial brain imaging	Not collected/ recorded	403							2				2	4
minor	ECG	Not collected/ recorded	405		8								2	1	11
MAJOR	alteplase details	Not collected/ recorded	406		2										2

MAJOR	Bolus dose	Incorrect bolus dose is given(Considering the expensive cost of opening another vial of alteplase, the acceptable rounding for total dose is ≤3mg. The acceptable bolus rounding is ≤0.4mg)	410	1		2	20		2	8			18	2	53
MAJOR	Infusion dose	Not collected/ recorded	411											2	2
MAJOR	Infusion dose	Incorrect infusion dose is given (Considering the expensive cost of opening another vial of alteplase, the acceptable rounding for total dose is ≤3mg)	412		1	1	20			12			12	2	48
minor	Last 5 digits of the batch number of vial	Not collected/ recorded	413	6	3	4	24			34			1	9	81
minor	Platelet count	Not collected/ recorded	418		2		3						18	1	24
minor	Platelet count	<100,000/microL (contraindication of alteplase)	419		2	1	7			2		1	5		18
minor	Red cell count	Not collected/ recorded	420		2	2	2						10	1	17
minor	Haemoglobin	Not collected/ recorded	421		2	2	2						10	1	17
minor	Haematocrit	Not collected/ recorded	422		2		2						10	1	15
minor	Leukocyte count	Not collected/ recorded	423		2	2	2						10	1	17
minor	INR	Not collected/ recorded	424		3	2	1						16	7	29
minor	INR	>1.8 (contraindication of alteplase)	425		1		3	1					6		11
minor	APTT (if received heparin)	Not collected/ recorded (Only for patients received heparin)	426				1						10	1	12

minor	Glucose	Not collected/ recorded	427		23	3		1		1			11	1	40
minor	Glucose	<2.8 mmol/L (50mg/dl) or >22.0mmol/L (396mg/dl) (contraindication)	428				3			1			4	2	10
minor	Creatinine	Not collected/ recorded	429		2	3	1			1			10	1	18
minor	Sodium	Not collected/ recorded	430		2	2	1	1		2			11	2	21
minor	Potassium	Not collected/ recorded	431		2	2	1	1		2			15	2	25
MAJOR	Date and time alteplase initiated	Alteplase treatment is commenced before randomisation for alteplase arm	432			2	1			12			2		17
minor	Last 5 digits of the batch number of vial	Package is not kept for monitoring	433	10	4	3	19			24			1		61
minor	GCS score @ 24 hours after randomisation	Not collected/ recorded	504				3								3
minor	NIHSS score @ 24 hours	Not collected/ recorded	505				1						1		2
minor	Repeat brain imaging	Not collected/ recorded	515	1	1		7	4					10	5	28
MAJOR	IV BP lowering medications	For intensive group, IV BP lowering medication is not given intensively to achieve the BP target and to maintain it for 72 hours according to the protocol	530	2			13		2				4		21
MAJOR	IV BP lowering medications	For conservative group, IV or intensive BP lowering medication is given even though patient's BP is below 180.	531				5								5
minor	Date GCS score taken	GCS score was taken outside of the time point	532			3	5						1		9
minor	Date NIHSS score taken	NIHSS score was taken outside of the time point	533			5	4						3		12

minor	GCS score @ discharge or day 3	Not collected/ recorded	600				1				1		3		5
minor	NIHSS score @ discharge or day 3	Not collected/ recorded	601				1				1		6		8
minor	mRS score @ 7days	Not collected/ recorded	602				1						4	1	6
MAJOR	Consent	Nil documented consent from either subject or PR at all	618	1			6			1					8
MAJOR	Consent	Nil documented consent from either PR or subject before randomisation - consent from PR/subject obtained post randomisation	619				1			4				1	6
MAJOR	Consent	Consent obtained by non-authorised site staff;	620	2			6						8		16
MAJOR	Consent	Consent given by non-authorised people;	621	2			1			1					4
minor	Consent	Missing original PIS_CF (photocopy only)	622							1					1
minor	Consent	Missing pages from executed PIS;	623	1											1
MAJOR	Consent	Missing subject signature: Subject didn't sign at all.	624	1											1
MAJOR	Consent	Missing subject name: when signature is not readable.	625										5		5
MAJOR	Consent	Missing subject date	626	1			3						5		9
MAJOR	Consent	Missing PR signature: PR didn't sign at all.	627							1					1
MAJOR	Consent	Missing PR name: when signature is not readable.	628										1		1
MAJOR	Consent	Missing PR date	629				3						1		4

MAJOR	Consent	Missing person obtaining consent signature: person obtaining consent didn't sign at all.	630				9	1					3		13
MAJOR	Consent	Missing person obtaining consent name: when signature is not readable.	631	1			2								3
MAJOR	Consent	Missing person obtaining consent date	632				6						2		8
MAJOR	Consent	Missing witness signature: Witness didn't sign at all	633	3			3			1	1				8
MAJOR	Consent	Missing witness date	634	2			2				1				5
minor	Consent	Patient information sheet case form (PIS_CF) copy not given to subject/PR	635				49						9		58
MAJOR	Consent	Date fields completed by person other than respective signatory;	636	7			2			1			5		15
minor	Consent	Other	638	19			67						93	2	181
MAJOR	Consent	PIS_CF not approved by ethics (original / amendment version affects subject safety)	639										1		1
minor	Consent	PIS_CF not approved by ethics (amendment does not affect subject safety)	640				5						22		27
minor	Consent	Expired PIS_CF (current version does not affect subject safety)	642				14			2		5	35		56
MAJOR	Consent	Witness is not independent of study	646	6											6
MAJOR	Consent	Declaration form signed by two members of study team (Declaration of 2 physicians, 1 should be independent of study)	647								1				1
minor	Consent	Name fields completed by person other than respective signatory.	648	6									5		11

minor	Consent	PR signed PIS_CF/ Patient signed PR_CF	649				2						2		4
minor	Consent	Missing subject signature: Subject signed in the wrong place.	650				4						12		16
minor	Consent	Missing subject name: when signature is readable.	651				5						10		15
minor	Consent	Missing PR signature: PR signed in the wrong place.	652				6			1			4	1	12
minor	Consent	Missing PR name: when signature is readable.	653				12								12
minor	Consent	Missing person obtaining consent signature: person obtaining consent signed in the wrong place.	654	1			7						1		9
minor	Consent	Missing person obtaining consent name: when signature is readable.	655				10								10
minor	Consent	Missing Witness signature: Witness signed in the wrong place.	656	1											1
minor	Date GCS score taken	GCS score was taken outside of the time point	659	3		3	11						5		21
minor	Date NIHSS score taken	NIHSS score was taken outside of the time point	660	3		3	11						9		26
minor	Date mRS score taken	mRS score was taken outside of the time point	661	3		2	9						6		20
MAJOR	BP recorded at set intervals	Not collected/ recorded	700										2		2

minor	BP recorded at set intervals	≥1 set interval data point/s not recorded by Day 7 inclusive or the day/time of discharge/death inclusive if prior to day 7. This deviation doesn't include missing BPs from alteplase initiation to randomisation for BP arm only patients, missing BPs after BP lowering treatment for alteplase arm only patients, missing BPs after BP lowering treatment for patients with no BP lowering treatment, and missing the additional BPs for the patients randomised in the protocol version 2.1 and 3.0.	701	5		1			1	73			23	11	114
minor	Date of 28 day assessment	Date of assessment outside window;	800	12	7	17	22	2	2	11	4		98	53	228
MAJOR	Date of 28 day assessment	Assessment not conducted	801	1	1					2			15		19
MAJOR	mRS score @ 28 days	Not completed	802										25		25
minor	EQ-5D mobility @ 28 days	Not completed	803										24		24
minor	EQ-5D self-care @ 28 days	Not completed	804										24		24
minor	EQ-5D usual activities @ 28 days	Not completed	805										24		24
minor	EQ-5D pain and discomfort @ 28 days	Not completed	806										24		24
minor	EQ-5D anxiety/depression @ 28 days	Not completed	807										25		25
MAJOR	Simplized mRS questions	Not recorded	808										23		23
minor	Any current BP lowering medications	Not collected/ recorded	810										24		24

minor	Any current aspirin or other anti-platelet therapy	Not collected/ recorded	811										23		23
minor	Any current HMG CoA reductase inhibitor (statin)	Not collected/ recorded	812										23		23
minor	Any readmissions to hospital or any recurrent vascular event	Not collected/ recorded	813										23		23
minor	Patient dwelling place	Not collected/ recorded	814										23		23
minor	Patient visited a hospital outpatient rehabilitation facility or therapist	Not collected/ recorded	815										27		27
minor	Whether the assessor knows what randomised treatments were given to the patient	Assessor is not blinded (excluding the situtation when the patient was dead)	817	4			38	2		4		3	60	1	112
minor	What number between 0-100 best describes the patient's health state today	Not completed	818		1					1			24		26
minor	Date of 90 day assessment	Date of assessment outside window;	900	7	1	3	7			4			60	29	111
MAJOR	Date of 90 day assessment	No attempt made for Day 90 follow up	901										2		2
MAJOR	mRS score @ 90 days	Not collected/ recorded	902	1						1			44		46
minor	EQ-5D mobility @ 90 days	Not collected/ recorded	903	1						1			41		43
minor	EQ-5D self-care @ 90 days	Not collected/ recorded	904	1						1			41		43
minor	EQ-5D usual activities @ 90 days	Not collected/ recorded	905	1						1			41		43
minor	EQ-5D pain and discomfort @ 90 days	Not collected/ recorded	906	1						1			42		44
minor	EQ-5D anxiety/depression @ 90 days	Not collected/ recorded	907	1						1			42		44

MAJOR	Simplized mRS questions	Not collected/ recorded	908							1			41		42
minor	Any current BP lowering medications	Not collected/ recorded	910							1			40		41
minor	Any current aspirin or other anti-platelet therapy	Not collected/ recorded	911							1			36		37
minor	Any current HMG CoA reductase inhibitor (statin)	Not collected/ recorded	912							1			36		37
minor	Any readmissions to hospital or any recurrent vascular event	Not collected/ recorded	913							1			41		42
minor	Patient dwelling place	Not collected/ recorded	914							1			40		41
minor	Patient visited a hospital outpatient rehabilitation facility or therapist	Not collected/ recorded	915							1			45		46
minor	Patient visited a hospital outpatient rehabilitation facility or therapist	Times not recorded	916										4		4
minor	Whether the assessor knows what randomised treatments were given to the patient	Assessor is not blinded (excluding the situtation when the patient was dead)	917	3			28	2		4		3	39	1	80
minor	What number between 0-100 best describes the patient's health state today	Not completed	918	1						2			41		43
MAJOR	SAE	Not reported within timeframe;	1001	4	2	2	33			37			23		100
MAJOR	Event onset date	Not collected/ recorded	1007										1		1
MAJOR	Resolution code	Not collected/ recorded	1020										1		1
MAJOR	Resolution date	Not collected/ recorded	1021										1		1
MAJOR	Confidentiality and Privacy	Breach of confidentiality/privacy	1101							2			25		27

MAJOR	Data Management	Inappropriate use of eCRF username/password by person other than person the username/password was assigned to	1102			1	6	1					2	1	11
MAJOR	Critical / Essential documents	Significant document missing @ completion of study	1103											1	1
minor	Miscellaneous	Miscellaneous	1105							2			56	22	80
MAJOR	Miscellaneous	Miscellaneous	1106										2		2
minor	Investigational Medicinal Product	Medication used is not from trial stock (for UK only) or Trial stock is used to non-Enchanted patient.	1107										18		16
Major	Patient lost to follow up	Patient lost to follow up, i.e. a patient whose survival status is unknown at Day 90 (Form G)	1108				1						13		14
			Total	**128**	**77**	**73**	**589**	**18**	**7**	**316**	**9**	**12**	**1849**	**183**	**3261**

9. Sample size calculations

Primary clinical outcome. The Cochrane reviews of thrombolysis in acute ischemic stroke note the rate of death or disability (mRS scores of 2-6) in patients treated with standard-dose iv alteplase as 50% and non-randomised studies suggest that low-dose alteplase provides similar clinical outcomes (i.e. risk ratio 1.0). For comparison between low- and standard-dose alteplase, a noninferiority margin is proposed based on the pooled Cochrane review where the overall risk ratio of standard-dose alteplase versus control with respect to death or disability was 0.76 (95%CI 0.66-0.87). Taking a conservative approach, the 40th percentile point around the risk reduction estimate (0.77) rather than the observed risk ratio is the more robust reference to describe the effects of standard-dose alteplase (translated into a margin of excess risk of placebo versus standard-dose alteplase of 1.29). The United States Food and Drug Administration (FDA) recommends that the clinical margin representing the largest acceptable inferiority can be set at 50% (i.e. risk ratio 1.14). Thus, a non-inferiority margin of 1.14 has been set in ENCHANTED to provide assurance that low-dose alteplase retains at least half the efficacy of standard-dose alteplase, provided the upper limit of 95% CI of low- versus standard-dose alteplase is less than this noninferiority margin. However, as there is potential for a negative interaction between intensive BP lowering and low-dose alteplase, the primary event rates have been set at 46.25% in patients receiving standard-dose alteplase and 46.75% in those receiving low-dose alteplase, making the absolute noninferiority margin 6.5%. A sample size of 3300 (1650 per group) was estimated to provide >90% power (1-sided α 0.025) to achieve the noninferiority setting, assuming 5% drop-out with the ability to also assess for superiority of low- versus standard-dose alteplase.

Secondary outcome of symptomatic intracerebral hemorrhage (sICH). The overall risk of standard-dose iv alteplase related sICH in the Cochrane review was 7%, with registries reporting frequencies of 4-10% depending on the definitions used. Observational studies of low-dose alteplase in Japan suggest lower risks of sICH (3-4%, risk reduction >40%). Based on the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR), an expected 15 mmHg systolic BP difference between randomised groups of BP lowering is likely to be associated with ≥40% reduction in sICH with standard-dose alteplase. Assuming a potential interaction between low-dose alteplase and intensive BP lowering, a more conservative 36% reduction is expected in patients receiving low-dose alteplase. Event rates are estimated to be 5.6% with the standard-dose alteplase and 3.44% with low-dose alteplase. The sample size of 3300 (1650 patients per group) was estimated to provide >80% power (2-sided α 0.05) to detect >40% relative reductions in sICH for the low-dose alteplase group, with 5% of drop-out.

10. Terms of reference of the Data Safety Monitoring Board (DSMB)

The DSMB was responsible for: safeguarding the interests of trial participants; assessing the safety and efficacy of the interventions during conduct of the trial; monitoring the overall conduct of the clinical trial; providing recommendations about stopping or continuing the trial to the Steering Committee; contributing to enhancing the integrity of the trial; formulating recommendations in relation to the selection, recruitment, or retention of participants, or their

management, or to improving their adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMB was advisory to the Steering Committee. The Steering Committee was responsible for promptly reviewing the DSMB recommendations, deciding as to whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct were required. The DSMB conducted both periodical safety reviews and formal interim analyses as follows:

- The safety reviews concentrated on safety assessment and did not include formal testing of the efficacy data;
- The date of each DSMB meeting was made available to the unblinded statisticians with at least 6 weeks notice;
- The trial Principal Investigator and other members of the Trial Operations Committee based at The George Institute attended open sessions at the beginning of meetings, and were available at the end of meetings to answer any urgent questions;
- The unblinded statisticians prepared the DSMB reports and attended the whole meeting to assist with interpretation of the results.

Safety reports were sent to the DSMB members every 6 months. No other safety reviews were conducted outside of twice annual meetings. The first analysis meeting of the DSMB occurred 6 months after the start of the study to review initial safety data and finalise the format of reports. Two further 'Formal Interim Analysis' meetings were held to review data relating to treatment efficacy, patient safety and quality of trial conduct when approximately 33% and 66% of randomised patients were included. All meetings were held by teleconference.

For each DSMB meeting, both safety reviews and interim analysis, Open and Closed Reports were provided. Open Reports, available to all who attended the DSMB meeting, include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up and compliance. Closed Reports, available only to those attending the Closed Sessions of the DSMB meeting, included analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of adverse events and symptom severity, and Open Report analyses that are displayed by intervention group. The reports for the safety reviews were a subset of the reports prepared for the formal interim analysis.

The unblinded statistician(s) from The George Institute prepare both the open and closed reports. The Open and Closed Reports provided information that was accurate, with follow-up that was complete to within approximately one month of the date of the DSMB meeting. The Reports were provided to DSMB members 1-2 weeks prior to the date of the meeting.

During the period of recruitment into the study, interim analyses of the proportion of patients alive and independent, or dead (at hospital discharge and at 3 months), or with other major outcome events were supplied, in strictest confidence, to all members of the DSMB, along with any other analyses that the DSMB may have requested. In the light of these analyses, the DSMB was charged with advising the Principal Investigator if, in their view, the randomized comparisons have provided both

(i) 'proof beyond reasonable doubt' that for all, or some, a treatment is clearly indicated or clearly contra-indicated and
(ii) evidence that might reasonably be expected to lead many clinicians conversant with the available evidence to materially change their practice with regard to either the choice of early intensive blood pressure lowering strategies or dose of alteplase in patients with acute ischemic stroke.

Criteria for stopping or modifying the trial for safety were considered on the balance of ensuring safety for trial participants and how early stopping would impact on clinical practice. The Haybittle-Peto rule was used as a guide for proof beyond reasonable doubt in the monitoring of both efficacy and safety information in the trial.

The DSMB worked on the principle that a difference of at least 3 SD in an interim analysis of a major outcome event (e.g. death from all causes or independent survival at 90 days) between patients allocated to intensive blood pressure lowering, conservative blood pressure lowering, low-dose alteplase and standard-dose alteplase, to justify halting, or modifying, the study before the planned completion of recruitment. This criterion (Peto rule) has the practical advantage that the exact number of interim analyses is of less importance, and so no fixed schedule is proposed.

The DSMB did not advise the Steering Committee about the need to modify entry to the study (or seek extra data), and as such the Steering Committee, collaborators and central project staff remained ignorant of the interim results.

11. Procedures and criteria used for the assessment of intracranial hemorrhage

CT scans (or MRIs) were conducted according to standardized techniques at baseline (i.e. for confirmation of the diagnosis) in all patients, and at 24-36 hours in as many patients as possible according to usual clinical practice. Further brain imaging and cerebral angiography were undertaken as part of usual clinical practice. Uncompressed digital CT, MRI and angiogram images were collected in DICOM format on a CD-ROM identified only with the patient's unique study number and uploaded by a special purpose-built web-based system for central analysis at The George Institute for Global Health.

The brain imaging scans were analyzed to assess for any intracranial hemorrhage according to the following procedures:

- All scans with an intracranial hemorrhage event reported by investigators as a serious adverse event were reviewed by two adjudicators;
- All follow-up scans without an intracranial event were reviewed by one adjudicator; those with intracranial hemorrhage detected were reviewed by a second adjudicator;
- 10% of baseline and other scans were reviewed by one adjudicator; those with intracranial hemorrhage detected were reviewed by a second adjudicator.

All scans with intracranial hemorrhage were assessed by at least 2 expert clinical scientists. If classification of the type of intracranial hemorrhage was consistent between readers, then the data were recorded directly to the database; if there was inconsistency, a third reader was

required to review and finalise the diagnosis and classification of intracranial hemorrhage, according to the following adjudication procedures:

Clinician scientists were to provide responses to the following questions:

1. Is there any evidence of hemorrhage on this scan? Yes/No

   If No, proceed to question 3

   If Yes, code bleeding as follows:

   a. HI1 Small petechiae along the margins of the ischemia/infarction
      Yes/No
   b. HI2 Confluent petechiae within infarcted area but no space occupying effect
      Yes/No
   c. PH1 Blood clots in <30% of infarcted area + slight space-occupying effect
      Yes/No
      Blood clots in >30% of infarcted area + substantial space-occupying effect
      Yes/No
   d. And to respond with a classification to following diagnosis:
      Subarachnoid hemorrhage Yes/No
      Intraventricular hemorrhage Yes/No
      Subdural hemorrhage Yes/No
      Other hemorrhage Yes/No

2. In your opinion, will this hemorrhage have been the predominant cause of the neurological worsening? Yes/No

3. Assessment of swelling.
   Is there any evidence of midline shift Yes/No

Abbreviations: HI denotes hemorrhagic infarction; PH, parenchymal hemorrhage

The brain imaging system allows assessment of abnormalities using computer-assisted multi-slice planimetric and voxel threshold techniques in MIStar version 3.2 (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia). The system was built to store securely over 10,000 images acquired on participants, with an adjudication system primarily for the recording of intracranial hemorrhage.

The key safety outcome was symptomatic intracerebral hemorhage (sICH), defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), as large local or remote parenchymal ICH (type 2, defined as greater than 30% of the infarcted area affected by hemorrhage with mass effect or extension outside the infarct) combined with neurological deterioration (≥4 points on the NIHSS) or leading to death within 36 hours. This was finalised after finalisation of the protocol and outlined in the Statistical Analysis Plan (SAP) prior to unblinding of the data.

Other adjudicated definitions of sICH will be used that included:

- the NINDS trial criteria of any ICH associated with neurological deterioration (≥1 point change in NIHSS score) from baseline or death within 24-36 hours;

- the European-Australian Cooperative Acute Stroke Study 2 (ECASS2) of any ICH with neurological deterioration (≥4 points on the NIHSS) from baseline or death within 24-36 hours;
- the third European-Australian Cooperative Acute Stroke Study (ECASS 3) of any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours, plus the adjudicators view was that the hemorrhage would have been the predominant cause of any neurological worsening;
- the third International Stroke Trial (IST 3) of any either significant ICH (local or distant from the infarct) or significant hemorrhagic transformation (HT) of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment, plus the adjudicators view that the hemorrhage would have been the predominant cause of any neurological worsening;
- fatal ICH, defined by any parenchymal ICH of type 2 and death within 7 days.
- any ICH identified by the adjudicators

The non-adjudicated diagnosis of ICH was clinician-reported ICH as a serious adverse event (SAE).

12. Protocol violations in use of alteplase

Patients who have one or more of the following protocol violations will be excluded from the per-protocol (PP) population:

- age <18 years
- final diagnosis not acute ischemic stroke
- systolic BP >185 mmHg (inclusion criteria blood pressure level)
- randomized >4.5 hours
- final diagnosis unknown/uncertain because of missing source documents or neuroimaging
- failure to receive alteplase at either the correct bolus or infusion dose
- failure to obtain a blind assessment of the 90-day outcome.

The range of alteplase doses considered 'low' or 'standard' are those above and below the mid-point between study doses, that is defined as <0.75 versus ≥0.75 mg/kg, respectively. For the per protocol analysis, the dose of alteplase was based primarily on measured body weight, either pre-randomisation or after admission to hospital; if these data are missing, estimated body weight will be used to define the dose of alteplase. Definitions for a protocol violation on alteplase dose are: low-dose outside 0.6-0.75 mg/kg range and standard-dose outside of 0.75-0.9mg/kg range.

13. Assessments of functional outcome and health-related quality of life

The primary outcome was the combined endpoint of death or disability at 90 days, defined by scores of 2 to 6 on the conventional modified Rankin scale (mRS), a global seven-level measure of functioning where scores 0 to 1 indicate a good outcome with minimal or no neurological symptoms, scores 2 to 5 indicate a poor outcome with increasing degree of disability, and death

is 6. The recently developed, simplified modified Rankin scale questionnaire (smRSq),[1,2] which requires only yes or no answers, was also used. For assessment of health-related quality of life (HRQoL), the EQ-5D questionnaire was used, as assessed directly by a patient or by a proxy-responder. The descriptive system of the EQ-5D defines the state of general health across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels (no problems, some/moderate problems, and severe problems). The EQ-5D utility score integrates the ratings of the 5 dimensions into a single score, calculated by using population-based preference weights for each subscale. In the present analysis, we used the weights obtained from the United Kingdom population. Utility scores express HRQoL quantitatively as a fraction of perfect health, with a score of 1 representing perfect health, a score of 0 representing death, and negative scores (minimum score -0.109) representing health states considered worse than death. The average utility score in disease-free populations range between 0.8 and 0.9.[3-6] When patients were not able to answer the questionnaire themselves, proxy-responders, such as their caregiver or doctor, were asked to rate the patient's HRQoL. The protocol did not stipulate specifically the process of proxy-responder selection; the decision was opportunistic that arose during a telephone or face-to-face interview between the responsible neurologically competent person (blinded to treatment arm) and the patient or caregiver at the scheduled time of follow-up.

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6. Sullivan PW, Ghushchyan V. Preference-based eq-5d index scores for chronic conditions in the united states. *Med Decis Making* 2006;26:410-420

13. Tables

Table S1. Reasons that patients with acute ischemic stroke were excluded from participating in the trial

1. In the United Kingdom, 64505 patients with acute ischemic were identified in the prospectively collected minimum data collection on all hospitalized patients with acute stroke collected as part of the Sentinel Stroke National Audit Program (SSNAP) for the study period. Of these, 54597 were considered eligible but were not given alteplase, while 9908 received alteplase outside of the trial.

2. Based on screening logs submitted from all hospital sites outside of the United Kingdom, the reasons for patients failing to meet inclusion criteria are outlined below

Reason	**Frequency**
Age <18 years	358
Systolic blood pressure >220mmHg	42
Unable to start treatment within 4.5 hour time window	2048
Unable to admit patient to a monitored facility	669
Contraindication to alteplase	128
Treated with alteplase outside of the trial	110
Structural brain abnormality	173
Other cause for ischemic stroke	37
Considered to be a high mortality risk	60
Advanced dementia or disability	1036
Concomitant medical illness	62
Refused	84
Participating in another clinical trial	11
Other	2
Total	**4820**

3. In addition, 13 patients were mistakenly randomized, and 10 had duplicate randomizations

Table S2. Characteristics of the patients at baseline and process measures in the per-protocol on treatment analysis set*

Variable	Low dose tPA (N=1492)	Standard dose t-PA (N=1484)
Demographic characteristic		
Age – yr		
Median	68	68
Interquartile interval	58-76	59-76
Female sex – no. (%)	568 (38.1)	551 (37.1)
Region of recruitment - no. (%)		
China	672 (45.0)	667 (44.9)
United Kingdom/Europe/Australia	368 (24.7)	368 (24.8)
Other Asia	301 (20.2)	303 (20.4)
South America	151 (10.1)	146 (9.8)
Asian ethnic group†	973 (65.2)	963 (64.9)
Medical history - no. (%)		
Hypertension	937 (62.8)	942 (63.5)
Any stroke	255 (17.1)	275 (18.5)
Coronary artery disease	234 (15.7)	214 (14.4)
Other heart disease	98 (6.6)	107 (7.2)
Atrial fibrillation confirmed on electrocardiogram	304 (20.4)	287 (19.3)
Diabetes mellitus	285 (19.1)	292 (19.7)
Hypercholesterolemia	253 (17.0)	227 (15.3)
Tobacco use‡	342 (23.0)	365 (24.6)
No symptoms on modified Rankin scale before stroke §	1225 (82.2)	1201 (80.9)
Medications - no. (%)		
Antihypertensive medication	681 (45.6)	671 (45.2)
Statin or other lipid lowering agent	283 (19.0)	259 (17.5)
Aspirin or other antiplatelet agent	362 (24.3)	314 (21.2)
Warfarin anticoagulation	39 (2.6)	28 (1.9)
Blood pressure– mm Hg		
Systolic	149±20	150±20
Diastolic	84±13	85±13
Severity of neurological deficit by scores on the NIHSS ¶		
Median	9	8
Interquartile interval	5-14	5-14
Level of consciousness by scores on the GCS‖		
Median	15	15
Interquartile interval	13-15	14-15
Brain imaging features - no. (%)**		
CT scan used	1449 (97.1)	1437 (96.8)
MRI scan used	195 (13.1)	191 (12.9)
Signs of cerebral ischemia	350 (23.5)	353 (23.8)
Final diagnosis at time of hospital separation - no. (%)††		
Large artery occlusion due to significant atheroma	588/1477 (39.8)	611/1464 (41.7)
Small vessel or perforation lacunar disease	321/1477 (21.7)	324/1464 (22.1)
Cardio-embolism	302/1477 (20.4)	292/1464 (19.9)
Dissection	13/1477 (0.9)	10/1464 (0.7)
Other or uncertain etiology	253/1477 (17.1)	227/1464 (15.5)
Treatment with IV alteplase		
Time from stroke onset to treatment - mins		
Median	172	170

Interquartile interval	129-219	128-219
Any given to patients - no. (%)	1492 (100.0)	1484 (100.0)
Bolus infusion dose - mg	6.2 ±1.2	6.3 ±1.2
Maintenance infusion dose - mg	35.1 ±6.6	56 ±10.8

*Plus-minus values are means ±SD. There were no significant differences between study groups except in the maintenance infusion dose of alteplase between the two study groups (P <0.0001). The term CT denotes computed tomography, CTA CT angiography, MRI magnetic resonance imaging, MRA magnetic resonance angiography, and IV intravenous

†Ethnicity is self-reported

‡Values reflect current use

§Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability or death

¶Scores on the National Institutes of Health stroke scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficits.

‖Scores on the Glasgow Coma Scale (GCS) range from 15 (normal) to 3 (deep coma)

**Values reflect features reported by clinician investigator on CT or MRI with any associated angiography

††Values reflect diagnosis reported by clinician investigator on the basis of investigations undertaken

Table S3a. Dosing of alteplase to participants

Variable	Low-dose alteplase (N=1654)	Standard-dose alteplase (N=1643)
Estimated body weight prior to alteplase - kg	69.6 ±14.4	69.9 ±14.4
Patients with measured body weight after use of alteplase	1495 (90.4)	1475 (89.8)
Measured body weight after use of alteplase - kg	69.2 ±14.5	69.4 ±14.4

Table S3b. Dosing of alteplase to participants, by major ethnic group

						Maximum dose achieved*	
Group	**N**	**Mean ±SD**	**Median (IQI)**	**Minimum**	**Maximum**	**N (%)**	**P value**
All participants							
Standard dose (n=1645)	1617	62.2 ±12.7	63 (54 to 70)	5.4	136.8	63 (3.9)	0.82
Low dose (n=1657)	1628	41.7 ±8.6	40.7 (36 to 48)	5.9	87.8	66 (4.1)	
Non-Asian participants							
Standard dose (n=1645)	600	67.6 ±13.8	67.5 (58.5 to 76.5)	5.4	136.8	55 (9.2)	0.85
Low dose (n=1657)	599	45.3 ±9.1	45.0 (39.0 to 51.5)	6.3	87.8	53 (8.9)	
Asian participants							
Standard dose (n=1645)	1017	59.1 ±10.8	58.6 (50.0 to 67.5)	17.2	90.0	8 (0.8)	0.78
Low dose (n=1657)	1029	39.5 ±7.5	39.0 (34.8 to 45.0)	5.9	70.0	13 (1.3)	

IQI denotes interquartile interval

*90 mg for standard dose and 60 mg for low dose alteplase

Table S4. Non-compliance with trial treatment protocol*

Outcome	Low dose alteplase (N=1654) n\N (%)	Standard dose alteplase (N=1643) n\N (%)	Total (N=3297) n\N (%)
Did not receive alteplase			
Total	26/1654 (1.6)	26/1643 (1.6)	52/3297 (1.6)
Clinical contraindication	11/1654 (0.7)	12/1643 (0.8)	23/3297 (0.7)
Family refused	6/1654 (0.4)	9/1643 (0.5)	15/3297 (0.5)
Rapid clinical improvement	9/1654 (0.5)	5/1643 (0.3)	14/3297 (0.4)
Randomization violations			
Acute stroke syndrome not ischemic	2/1654 (0.1)	1/1643 (0.1)	3/3297 (0.1)
Dependent pre-stroke	6/1654 (0.4)	8/1643 (0.5)	14/3297 (0.4)
Significant comorbid condition	12/1654 (0.7)	12/1643 (0.7)	24/3297 (0.7)
Other	15/1654 (0.9)	14/1643 (0.9)	29/3297 (0.9)
Treatment compliance with alteplase			
Given beyond 4.5 hours	8/1654 (0.5)	14/1643 (0.9)	22/3297 (0.7)
Treatment protocol not followed	70/1654 (4.2)	63/1643 (3.8)	133/3297 (4.0)
Dose outside range	56/1654 (3.4)	44/1643 (2.7)	100/3297 (3.0)
Low dose in standard arm	-	19/1643 (1.2)	19/3297 (0.6)
High dose in low dose arm	13/1654 (0.8)	-	13/3297 (0.4)
Missing date and time of alteplase	26/1654 (1.6)	23/1643 (1.4)	49/3297 (1.5)
Final diagnosis			
Not ischemic stroke	50/1654 (3.0)	47/1643 (2.9)	97/3297 (2.9)
Outcome assessment at 90-days			
Assessor predicted treatment allocation	38/1506 (2.5)	33/1470 (2.2)	71/2976 (2.4)

*categories are not mutually exclusive.

Table S5. Management details from randomisation to Day 7*

	Low dose group (N=1654)	Standard dose group (N=1643)	P value
Cerebral angiogram undertaken, n/N (%)	90/1648 (5.5)	81/1640 (4.9)	0.50
Occluded cerebral vessel identified, n/N (%)	81/90 (90.0)	70/80 (87.5)	0.61
Thrombectomy device/procedure used, n/N (%)	64/90 (71.1)	60/81 (74.1)	0.67
Solitiare	51/64 (79.7)	46/60 (76.7)	
Penumbra	6/64 (9.4)	6/60 (10.0)	
Angioplasty	2/64 (3.1)	1/60 (1.7)	
Merci	1/64 (1.6)	-	
Other	4/64 (6.3)	7/60 (11.7)	
Intra-arterial alteplase used, n/N (%)	16/90 (17.8)	9/80 (11.3)	0.23
Alternative intra-arterial thrombolytic used, n/N (%)	5/90 (5.6)	3/79 (3.8)	0.59
Recanalization of cerebral vessel achieved, n/N (%)	57/89 (64.0)	51/80 (63.8)	0.97
Any IV BP lowering treatment in first 24 hours, n/N (%)	387/1643 (23.6)	406/1628 (24.9)	0.36
Any IV BP lowering treatment in days 2-7, n/N (%)	302/1626 (18.6)	310/1608 (19.3)	0.61
Systolic BP at 24 hours, mmHg	137±19	137±20	0.87
Intubation and ventilation, n/N (%)	79/1627 (4.9)	91/1607 (5.7)	0.30
Fever occurrence, n/N (%)	292/1627 (17.9)	327/1606 (20.4)	0.08
Fever treated, n/N (%)	240/1431 (16.8)	278/1433 (19.4)	0.07
Nasogastric feeding given, n/N (%)	282/1627 (17.3)	301/1606 (18.7)	0.30
Patient mobilized by therapist, n/N (%)	748/1627 (46.0)	706/1606 (44.0)	0.25
Compression stockings used, n/N (%)	151/1626 (9.3)	132/1606 (8.2)	0.28
Subcutaneous heparin used, n/N (%)	336/1654 (20.3)	291/1643 (17.7)	0.06
Any antithrombotic agent used in first 24 hours, n/N (%)†	307/1648 (18.6)	265/1634 (16.2)	0.07
IV traditional Chinese medicine administered, n/N (%)	474/1627 (29.1)	465/1606 (29.0)	0.91
IV steroids administered, n/N (%)	41/1627 (2.5)	36/1606 (2.2)	0.60
Hemicraniectomy performed, n/N (%)	17/1627 (1.0)	18/1607 (1.1)	0.84
Any neurosurgery performed, n/N (%)	57/1654 (3.4)	57/1643 (3.5)	0.97
Any stroke unit admission, n/N (%)	986/1627 (60.6)	991/1607 (61.7)	0.53
Any intensive care unit admission, n/N (%)	387/1627 (23.8)	385/1606 (24.0)	0.90

	Low dose group (N=1654)	Standard dose group (N=1643)	P value
Any rehabilitation given, n/N (%)	837/1627 (51.4)	804/1607 (50.0)	0.42
Decision to withdrawal active care, n/N (%)	41/1627 (2.5)	44/1608 (2.7)	0.70

*Plus-minus values are means ±SD. The term BP denotes blood pressure, IV intravenous.

†refers to use of aspirin or heparin/heparinoid.

Table S6. Source of information on outcome assessments

	Low dose group (N=1654)	Standard dose group (N=1643)	P value
28-day assessment			
In-person, n (%)	355 (23.8)	348 (22.8)	0.65
Phone to patient, n (%)	638 (42.7)	646 (42.4)	
Phone to caregiver, n (%)	434 (29.0)	460 (30.2)	
Phone to patient's doctor or medical practitioner, n (%)	23 (1.5)	32 (2.1)	
Other, n (%)	45 (3.0)	39 (2.6)	
90-day assessment			
In-person, n (%)	209 (14.5)	193 (13.0)	0.59
Phone to patient, n (%)	672 (46.5)	716 (48.1)	
Phone to caregiver, n (%)	520 (36.0)	526 (35.3)	
Phone to patient's doctor or medical practitioner, n (%)	15 (1.0)	19 (1.3)	
Other, n (%)	28 (1.9)	36 (2.4)	

Table S7. Mean (SD) systolic blood pressure readings by alteplase dose treatment group

Time	Low-dose alteplase (n=1654)			
	Intensive BP (n= 224) (13.5%)	Standard BP (n=236) (14.3%)	Difference	P value
At randomisation - n, mean (SD))	224 164.2 (10.0)	236 163.9 (10.1)	-0.3 (10.1)	0.75
At 1 hour - n, mean (SD)	221 142.8 (15.7)	229 151.8 (18.2)	9.0 (17.0)	<0.001
At 6 hours - n, mean (SD)	224 139.4 (16.7)	230 146.0 (18.0)	6.6 (17.4)	<0.001
At 24 hours - n, mean (SD)	217 140.6 (16.1)	227 143.8 (18.4)	3.3 (17.3)	0.05

Time	Standard-dose alteplase (1643)			
	Intensive BP (n=232) (14.1%)	Standard BP (n=246) (15.0%)	Difference	P value
At randomisation - n, mean (SD)	232 165.1 (9.6)	243 165.3 (10.1)	0.2 (9.9)	0.83
At 1 hour - n, mean (SD)	223 145.6 (17.9)	239 153.3 (16.6)	7.7 (17.3)	<0.001
At 6 hours - n, mean (SD)	224 139.2 (14.6)	241 148.3 (17.6)	9.0 (16.2)	<0.001
At 24 hours - n, mean (SD)	219 141.9 (16.1)	238 145.0 (19.0)	3.1 (17.7)	0.06

Time	Overall (n=3297)			
	Intensive BP (n=476)	Standard BP (n=482)	Difference	P value
At randomisation - n, mean (SD)	456 164.7 (9.8)	479 164.6 (10.2)	-0.1 (10.0)	0.94
At 1 hour - n, mean (SD)	444 144.2 (16.9)	468 152.6 (17.4)	8.4 (17.1)	<0.001
At 6 hours - n, mean (SD)	448 139.3 (15.7)	471 147.2 (17.8)	7.9 (16.8)	<0.001
At 24 hours - n, mean (SD)	436 141.3 (16.1)	465 144.4 (18.7)	3.2 (17.5)	0.006

Table S8. Post-hoc assessment of the primary outcome according to the simplified modified Rankin scale questionnaire (smRSq)

Outcome	Low-dose alteplase (N=1654)	Standard-dose alteplase (N=1643)	Total (N=3297)	Odds Ratio with low-dose alteplase (95%CI)	P value†	P value‡
Death or disability - smRSq score 2 to 6 - no./total no. (%)						
Unadjusted	886/1609 (55.1)	863/1600 (53.9)	1749/3209 (54.5)	1.05 (0.91 to 1.20)	0.52	0.23
Adjusted §	883/1603 (55.1)	861/1597 (53.9)	1744/3200 (54.5)	1.06 (0.91 to 1.23)	0.48	0.34
Adjusted Per Protocol	815/1489 (54.7)	800/1482 (54.0)	1615/2971 (54.4)	1.05 (0.89 to 1.23)	0.57	0.30
Unadjusted category scores on the smRSq no./total no. (%)						
0 (no symptoms at all)	529/1609 (32.9)	538/1600 (33.6)	1067/3209 (33.3)	0.98 (0.87 to 1.11)	0.73	0.02
1 (no significant disability despite symptoms)	194/1609 (12.1)	199/1600 (12.4)	393/3209 (12.2)			
2 (slight disability)	132/1609 (8.2)	127/1600 (7.9)	259/3209 (8.1)			
3 (moderate disability requiring some help)	348/1609 (21.6)	291/1600 (18.2)	639/3209 (19.9)			
4 (moderate-severe disability requiring assistance with daily living)	124/1609 (7.7)	125/1600 (7.8)	249/3209 (7.8)			
5 (severe disability, bed-bound and incontinent)	142/1609 (8.8)	150/1600 (9.4)	292/3209 (9.1)			
6 (death at 90 days)	140/1609 (8.7)	170/1600 (10.6)	310/3209 (9.7)			
Adjusted category scores on the smRSq no./total no. (%) §						
0 (no symptoms at all)	527/1603 (32.9)	538/1597 (33.7)	1065/3200 (33.3)	0.97 (0.85 to 1.10)	0.61	0.01
1 (no significant disability despite symptoms)	193/1603 (12.0)	198/1597 (12.4)	391/3200 (12.2)			
2 (slight disability)	132/1603 (8.2)	127/1597 (8.0)	259/3200 (8.1)			
3 (moderate disability requiring some help)	346/1603 (21.6)	291/1597 (18.2)	637/3200 (19.9)			
4 (moderate-severe disability requiring assistance with daily living)	124/1603 (7.7)	124/1597 (7.8)	248/3200 (7.8)			
5 (severe disability, bed-bound and incontinent)	141/1603 (8.8)	150/1597 (9.4)	291/3200 (9.1)			
6 (death at 90 days)	140/1603 (8.7)	169/1597 (10.6)	309/3200 (9.7)			
Adjusted category scores on the smRSq in per-protocol population §						
0 (no symptoms at all)	496/1489 (33.3)	493/1482 (33.3)	989/2971 (33.3)	0.95 (0.84 to 1.09)	0.48	0.01
1 (no significant disability despite symptoms)	178/1489 (12.0)	189/1482 (12.8)	367/2971 (12.4)			
2 (slight disability)	125/1489 (8.4)	115/1482 (7.8)	240/2971 (8.1)			
3 (moderate disability requiring some help)	307/1489 (20.6)	269/1482 (18.2)	576/2971 (19.4)			
4 (moderate-severe disability requiring assistance with daily living)	118/1489 (7.9)	116/1482 (7.8)	234/2971 (7.9)			
5 (severe disability, bed-bound and incontinent)	136/1489 (9.1)	138/1482 (9.3)	274/2971 (9.2)			
6 (death at 90 days)	129/1489 (8.7)	162/1482 (10.9)	291/2971 (9.8)			

*CI denotes confidence interval, smRS simplified modified Rankin scale.

†Value for the low-dose as compared with the standard-dose group

‡Value for the noninferiority margin of 1.14, with a one-sided alpha level of 0.025

§Adjusted analysis includes minimization variables plus NIHSS score, time from the onset of symptoms to randomization and baseline variables of age, sex, ethnicity, premorbid mRS (0 or 1), prior use of aspirin or other antiplatelet agent or warfarin anticoagulation, and any history of stroke, coronary artery disease, diabetes mellitus or atrial fibrillation.

Table S9. Distribution of categories on the modified Rankin scale (mRS) between low dose and standard dose alteplase using the assumption-free statistical method of Howard*

		Standard dose alteplase					
	mRS categories	0 (n=397)	1 (n=385)	2 (n=225)	3 (n=181)	4 (n=154)	5+6 (n=257)
Low dose alteplase	0 (n=403)	159991	155155	90675	72943	62062	103571
	1 (n=349)	138553	134365	78525	63169	53746	89693
	2 (n=250)	99250	96250	56250	45250	38500	64250
	3 (211)	83767	81235	47475	38191	32494	54227
	4 (n=165)	65505	63525	37125	29865	25410	42405
	5+6 (n=229)	90913	88165	51525	41449	35266	58853

Total number of pairs with lower score ('better outcome') for low dose alteplase than standard dose alteplase = 1046665

Total number of pairs with higher score ('worse outcome') for low dose alteplase than standard dose alteplase = 1049868

Total number of ties = 473060

Outcome	**Better**	**Same**	**Worse**	**Ratio (better) / (better+worse)**
Percentage	40.7%	18.4%	40.9%	0.49924

P value of permutation 0.951

That is, no statistical significance is shown for low dose to be better than standard dose alteplase

*Howard G, Waller JL, Voeks JH, et al. A simple, assumption-free, and clinical interpretable approach for analysis of modified Rankin outcomes. Stroke 2012;43:664-669.

The assumption-free approach considers all possible pairs of observations where the first observation is taken from the low-dose group (Y_T) and the second observation is taken from the standard-dose (control) group Y_C. If group Y_T included *n* observations and group included *m* observations, the two-group comparison would lead to the total of *n x m* pairs of observations. In each pair, the observation from the treatment group will either be worse than the control observation, the same as the control observation, or better than the control observation. The probabilities that in a randomly chosen pair of treatment and control patients, the treatment patients has worse outcome ($Prob\ (Y_T > Y_C)$), the same outcome ($Prob\ (Y_T + Y_C)$) or better outcome ($Prob\ (Y_T < Y_C)$), can then be estimated as the ratio of the number of pairs satisfying each of these individual conditions to the total number of n x m pairs.

The permutation test first calculates a 'test statistic' for the observed data. In our study, we tested how far the observed proportion of non-tied pairs was from the null-hypothesis of 50%. The permutation test randomly assigned treatments to individuals, ensuring no association between treatment and the test statistic (guaranteeing the null hypothesis is true). This process was repeated 10,000 times, and the distribution of the test statistic under the null hypothesis was estimated. Whether the observed test statistic is *unusual* under the null hypothesis (that is, the P value) is simply the location of the observed test statistic in distribution of test statistics under the null hypothesis.

Table S10. Other secondary outcomes up to 3 months*

Outcome	Low-dose alteplase (N=1654)	Standard-dose alteplase (N=1643)	Odds Ratio with low-dose alteplase (95% CI)	P Value†	P Value‡
Efficacy					
Death or disability: mRS score 2 to 6 - no./total no. (%) §					
Adjusted ¶	853/1601 (53.3)	815/1596 (50.9)	1.13 (0.97 to 1.31)		0.88
Adjusted per protocol‖	796/1489 (53.5)	761/1482 (51.3)	1.13 (0.96 to 1.32)		0.89
Secondary					
Symptomatic intracerebral hemorrhage – no. (%)‡‡					
ECASS 2 criteria	55/1654 (3.3)	87/1643 (5.3)	0.62 (0.44 to 0.87)	0.006	
ECASS 3 criteria	20/1654 (1.2)	42/1643 (2.6)	0.47 (0.27 to 0.80)	0.005	
IST 3 criteria	33/1654 (2.0)	51/1643 (3.1)	0.68 (0.29 to 0.99)	0.05	
Fatal within 7 days	9/1654 (0.5)	24/1643 (1.5)	0.37 (0.17 to 0.80)	0.01	
Any intracerebral hemorrhage – no. (%)	277/1654 (16.7)	294/1643 (17.9)	0.92 (0.77 to 1.11)	0.38	
Adjusted ordinal analysis of category scores on the mRS - no./total no. (%)**					
0 (no symptoms at all)	402/1601 (25.1)	397/1596 (24.9)	0.99 (0.88 to 1.13)		0.03
1 (no significant disability despite symptoms)	346/1601 (21.6)	384/1596 (24.1)			
2 (slight disability)	250/1601 (15.6)	225/1596 (14.1)			
3 (moderate disability requiring some help)	165/1601 (13.1)	181/1596 (11.3)			
4 (moderate-severe disability requiring assistance with daily living)	160/1601 (10.3)	153/1596 (9.6)			
5 (severe disability, bed-bound and incontinent)	88/1601 (5.5)	87/1596 (5.5)			
6 (death)	140/1601 (8.7)	169/1596 (10.6)			
Adjusted shift in scores on the mRS per protocol - no./total no. (%) ¶**					
0 (no symptoms at all)	365/1489 (24.5)	361/1482 (24.4)	1.00 (0.88 to 1.14)		0.05
1 (no significant disability despite symptoms)	328/1489 (22.0)	360/1482 (24.3)			
2 (slight disability)	232/1489 (15.6)	210/1482 (14.2)			
3 (moderate disability requiring some help)	191/1489 (12.8)	165/1482 (11.1)			
4 (moderate-severe disability requiring assistance with daily living)	160/1489 (10.7)	145/1482 (9.8)			
5 (severe disability, bed-bound and incontinent)	84/1489 (5.6)	79/1482 (5.3)			
6 (death)	129/1489 (8.7)	162/1482 (10.9)			

Death or dependency: mRS score 3 to 6 - no./total no. (%)	605/1607 (37.6)	592/1599 (37.0)	1.03 (0.89 to 1.19)		0.15
Death during follow-up					
At 7 days	60/1654 (3.6)	87/1643 (5.3)	0.67 (0.48 to 0.94)	0.02	
Death or neurological deterioration in the first 24 hours – no. (%)‡‡	128/1654 (7.7)	141/1643 (8.6)	0.89 (0.70 to 1.15)	0.38	

*CI denotes confidence interval, ECASS 2, the second European-Australian Cooperative Acute Stroke Study, ECASS 3, the third ECASS, IST 3 third International Stroke Trial, mRS modified Rankin scale, NINDS National Institutes of Neurological Diseases and Stroke, NIHSS National Institute of Health Stroke Scale.

†Value for the low-dose as compared with the standard-dose group

‡Value for the noninferiority margin of 1.14, with a one-sided alpha level of 0.025

§The mRS evaluates overall function; scores range from 0 (no symptoms) to 6 (death). A score of 2 to 5 indicates some degree of disability.

¶Adjusted analysis includes minimization variables plus NIHSS score, time from the onset of symptoms to randomization and baseline variables of age, sex, ethnicity, premorbid mRS (0 or 1), prior use of aspirin or other antiplatelet agent or warfarin anticoagulation, and any history of stroke, coronary artery disease, diabetes mellitus or atrial fibrillation.

‖The primary analysis was performed in the as-treated, per-protocol population

** Symptomatic intracerebral hemorrhage was defined according to several criteria through central adjudication. The primary measure was according to SITS-MOST, where there was a large local or remote parenchymal intracerebral hemorrhage (type 2, defined as greater than 30% of the infarcted area affected by hemorrhage with mass effect or extension outside the infarct) in combination with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours. Other measures were the NINDS trial criteria, where there was any intracerebral hemorrhage with neurological deterioration (≥1 point on the NIHSS) from baseline or death within 36 hours; the ECASS 2 of any intracerebral hemorrhage with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours; the ECASS 3 of any intracerebral hemorrhage with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours; the IST 3 of any either significant intracerebral hemorrhage (local or distant from the infarct) or significant hemorrhagic transformation (HT) of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment; fatal intracerebral hemorrhage by any parenchymal intracrerebral hemorrhage (type 2) within seven days of treatment; and any intracerebral haemorrhage identified on brain imaging.

††The common odds was estimated from an ordinal logistic-regression model and indicates the odds of improvement of 1 point on the mRS, with a common odds ratio greater than 1 favouring standard-dose alteplase

‡‡Early neurological deterioration was defined as an increase from baseline of ≥4 on the NIHSS

Table S11. Causes of death during follow-up to 3 months

Diagnosis	Low dose alteplase (N=1654)	Standard dose alteplase (N=1643)	Total (N=3297)	Odds Ratio with low dose alteplase (95% CI)	P value
Direct effects of the acute ischemic stroke, n (%)	63 (3.8)	62 (3.8)	124 (3.8)	1.03 (0.72 to 1.47)	0.89
Acute intracerebral hemorrhage, n (%)	14 (0.8)	30 (1.8)	44 (1.3)	0.46 (0.24 to 0.87)	0.02
Recurrent stroke, n (%)					
Acute intracerebral hemorrhage	1 (0.1)	2 (0.1)	3 (0.1)	0.50 (0.04 to 5.48)	0.57
Acute ischemic stroke	6 (0.4)	3 (0.2)	9 (0.3)	1.99 (0.50 to 7.97)	0.33
Undifferentiated stroke	2 (0.1)	2 (0.1)	4 (0.1)	0.99 (0.14 to 7.06)	0.10
Acute coronary event, n (%)	3 (0.2)	6 (0.4)	9 (0.3)	0.50 (0.12 to 1.99)	0.33
Other vascular, n (%)	26 (1.6)	27 (1.6)	56 (1.7)	0.92 (0.54 to 1.57)	0.77
Non-vascular, n (%)	25 (1.5)	38 (2.3)	67 (2.0)	0.62 (0.38 to 1.02)	0.06
Pneumonia	16	23	39		
Sepsis	3	8	11		
Cancer	2	4	6		
Other	4	3	7		

CI denoted confidence interval

Table S12. Serious adverse events (SAEs) to the close of study*

Outcome	Low dose alteplase (N=1654) n (%)	Standard dose alteplase (N=1643) n (%)	Total (N=3297) n (%)	Odds Ratio with low dose alteplase (95% CI)	P value
All SAEs					
Events (including deaths)	559	627	1186		
Fatal events	159	190	349		
Non-fatal events	400	437	837		
Subjects with any SAE	415 (25.1)	448/1643 (27.3)	863/3297 (26.2)	0.89 (0.76 to 1.04)	0.16
All events					
Subarachnoid hemorrhage	4 (0.2)	3 (0.2)	7 (0.2)	1.33 (0.30 to 5.93)	0.71
Intracerebral hemorrhage	135 (8.2)	152 (9.3)	287 (8.7)	0.87 (0.68 to 1.11)	0.27
Extracranial hemorrhage	19 (1.1)	23 (1.4)	42 (1.3)	0.82 (0.44 to 1.51)	0.52
Ischemic stroke	118 (7.1)	97 (5.9)	215 (6.5)	1.22 (0.93 to 1.62)	0.15
Undifferentiated stroke	20 (1.2)	28 (1.7)	48 (1.5)	0.71 (0.40 to 1.26)	0.24
Acute coronary syndrome	21 (1.3)	19 (1.2)	40 (1.2)	1.10 (0.59 to 2.05)	0.77
Other vascular event	55 (3.3)	64 (3.9)	119 (3.6)	0.85 (0.59 to 1.22)	0.38
Pneumonia	63 (3.8)	71 (4.3)	134 (4.1)	0.88 (0.62 to 1.24)	0.46
Sepsis	27 (1.6)	32 (1.9)	59 (1.8)	0.84 (0.50 to 1.40)	0.50
Fracture	2 (0.1)	1 (0.1)	3 (0.1)	1.99 (0.18 to 21.94)	0.58
Other non-vascular	39 (2.4)	63(3.8)	102 (3.1)	0.61 (0.40 to 0.91)	0.02
Angioedema	4 (0.2)	6 (0.4)	10	0.66 (01.9 to 2.35)	0.52
Other	6 (0.4)	14 (0.9)	20	0.42 (0.16 to 1.11)	0.08
Fatal					
Subjects with a fatal SAE	141 (8.5)	172 (10.5)	313 (9.5)	0.80 (0.63 to 1.01)	0.06
Subarachnoid hemorrhage	1 (0.1)	2 (0.1)	3 (0.1)	0.50 (0.04 to 5.48)	0.57
Intracerebral hemorrhage	22 (1.3)	41 (2.5)	63 (1.9)	0.53 (0.31 to 0.89)	0.02
Extracranial hemorrhage	4 (0.2)	2 (0.1)	6 (0.2)	1.99 (0.36 to 10.87)	0.43
Ischemic stroke	61 (3.7)	45 (2.7)	106 (3.2)	1.36 (0.92 to 2.01)	0.12
Undifferentiated stroke	3 (0.2)	5 (0.3)	8 (0.2)	0.60 (0.14 to 2.49)	0.48

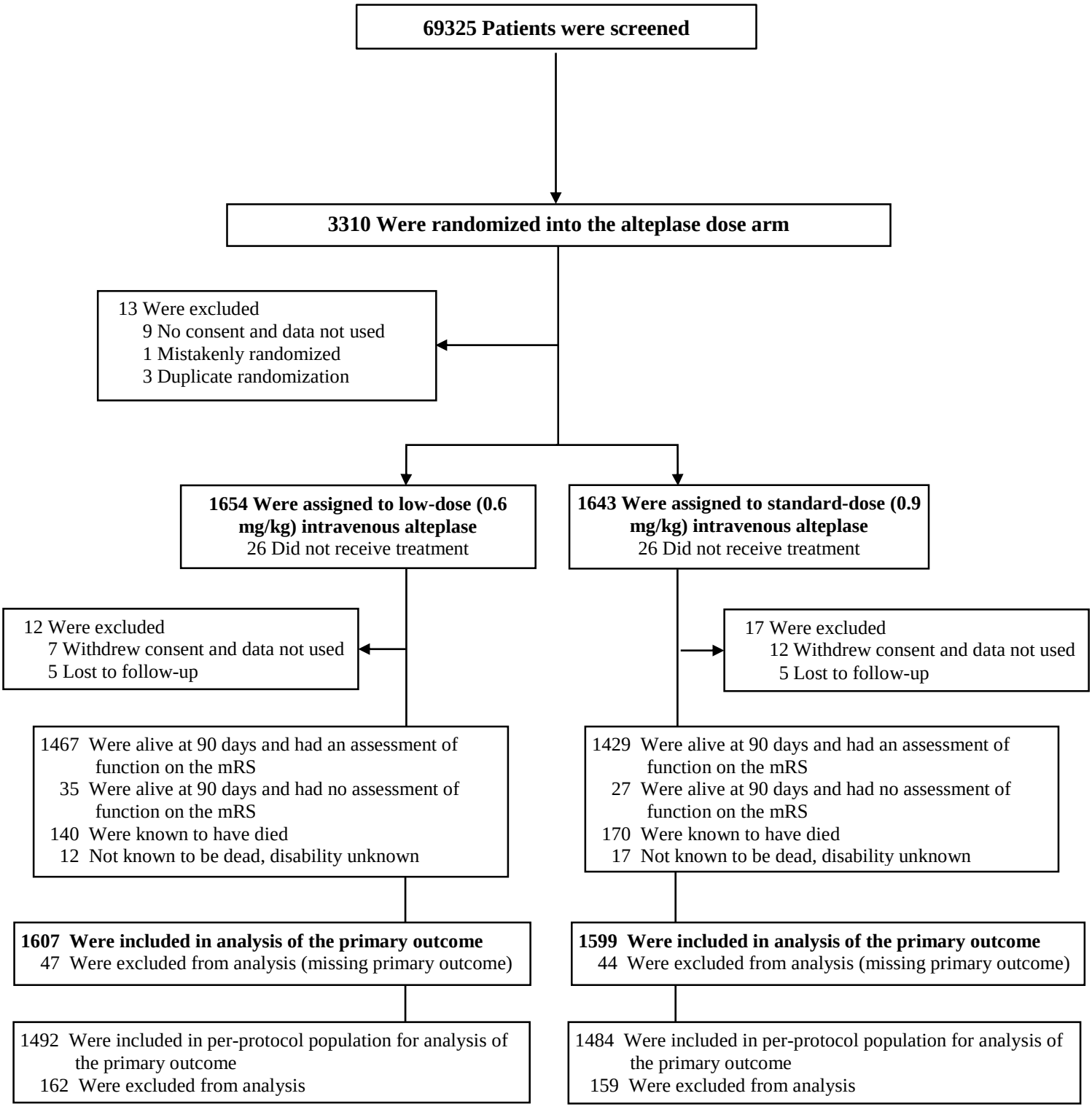
Outcome	Low dose alteplase (N=1654) n (%)	Standard dose alteplase (N=1643) n (%)	Total (N=3297) n (%)	Odds Ratio with low dose alteplase (95% CI)	P value
Acute coronary syndrome	7 (0.4)	13 (0.8)	20 (0.6)	0.53 (0.21 to 1.34)	0.18
Other vascular	16 (1.0)	14 (0.9)	30 (0.9)	1.14 (0.55 to 2.24)	0.73
Pneumonia	28 (1.7)	35 (2.1)	63 (1.9)	0.79 (0.48 to 1.31)	0.36
Sepsis	4 (0.2)	12 (0.7)	16 (0.5)	0.33 (0.11 to 1.02)	0.06
Fracture	-	-	-		
Other non-vascular	7 (0.4)	11 (0.7)	18 (0.5)	0.63 (0.24 to 1.63)	0.34
Angioedema					
Other SAE					
Non-Fatal					
Subjects with a non-fatal SAE	301 (18.2)	313 (19.1)	614 (18.6)	0.95 (0.79 to 1.13)	0.53
Subarachnoid hemorrhage	3 (0.2)	1 (0.1)	43 (0.1)	2.98 (0.31 to 28.71)	0.34
Intracerebral hemorrhage	113 (6.8)	111 (6.8)	224 (6.8)	1.01 (0.77 to 1.33)	0.93
Extracranial hemorrhage	15 (0.9)	21 (1.3)	36 (1.1)	0.71 (0.36 to 1.38)	0.31
Ischemic stroke	58 (3.5)	53 (3.2)	111 (3.4)	1.09 (0.75 to 1.59)	0.66
Undifferentiated stroke	17 (1.0)	23 (1.4)	40 (3.4)	0.73 (0.39 to 1.37)	0.33
Acute coronary syndrome	14 (0.8)	7 (0.84)	21 (0.6)	2.00 (0.80 to 4.96)	0.14
Other vascular	40 (2.4)	51 (3.1)	91 (2.8)	0.77 (0.51 to 1.18)	0.23
Pneumonia	39 (2.4)	40 (2.4)	79 (2.4)	0.97 (0.62 to 1.51)	0.89
Sepsis	23 (1.4)	21 (1.3)	44 (1.3)	1.09 (0.60 to 1.98)	0.78
Fracture	2 (0.1)	1 (0.1)	3 (0.1)	1.99 (0.18 to 21.94)	0.58
Other non-vascular	32 (1.9)	53 (3.2)	85 (2.6)	0.59 (0.38 to 0.92)	0.02
Angioedema	4 (0.2)	6 (0.4)	10 (0.3)	0.66 (0.19 to 2.35)	0.52
Other SAE	6 (0.4)	14 (0.9)	20 (0.6)	0.42 (0.16 to 1.11)	0.08

The term SAE denotes serious adverse event, and CI confidence interval

*Some SAEs were reported after the Day-90 assessment before data lock for close of the study

14. Figures

Fig. S1. Eligibility, randomization and follow-up of patients



mRS denotes modified Rankin scale

Figure S2. **Distribution of dose of alteplase based on measured body weight, by randomized group**

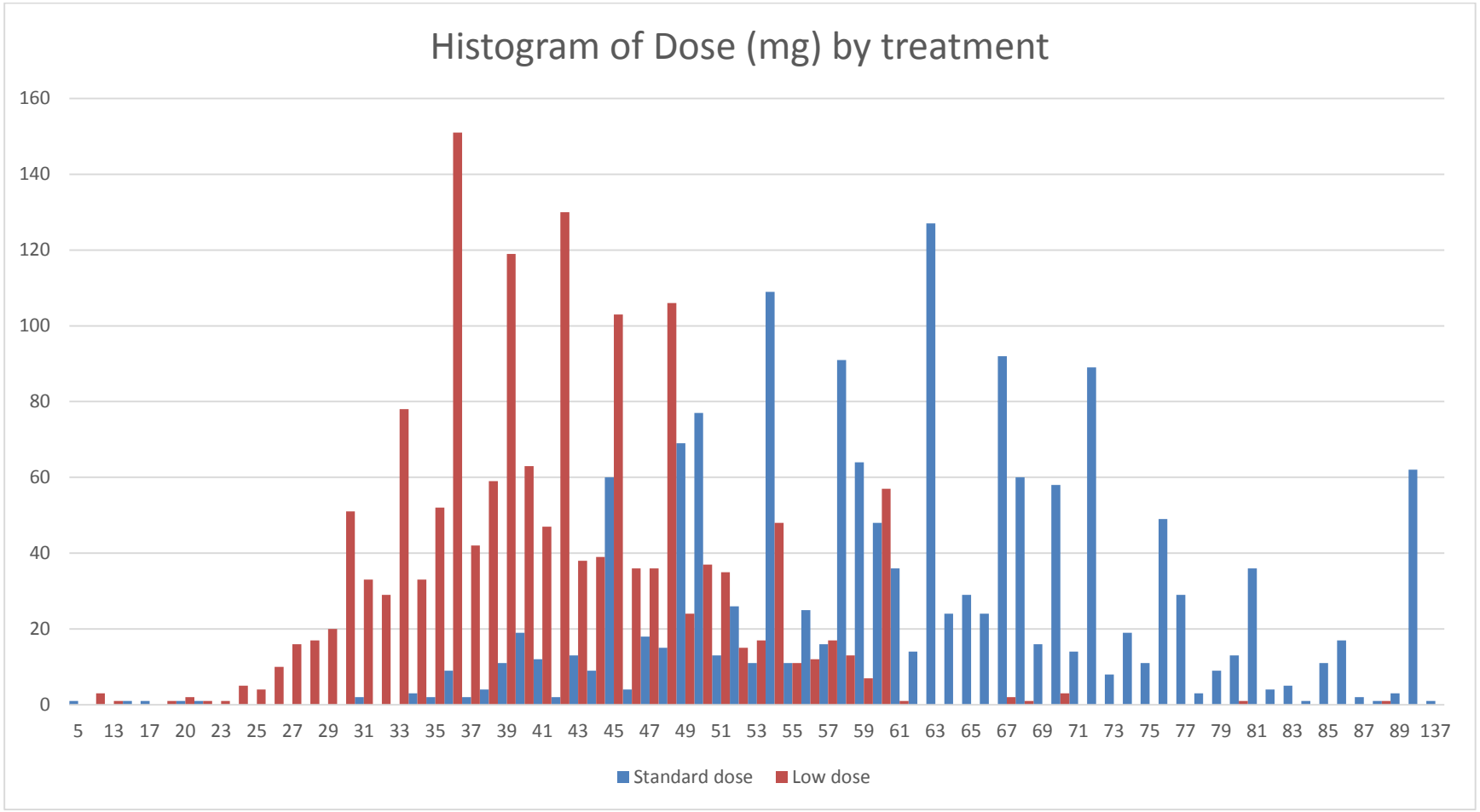
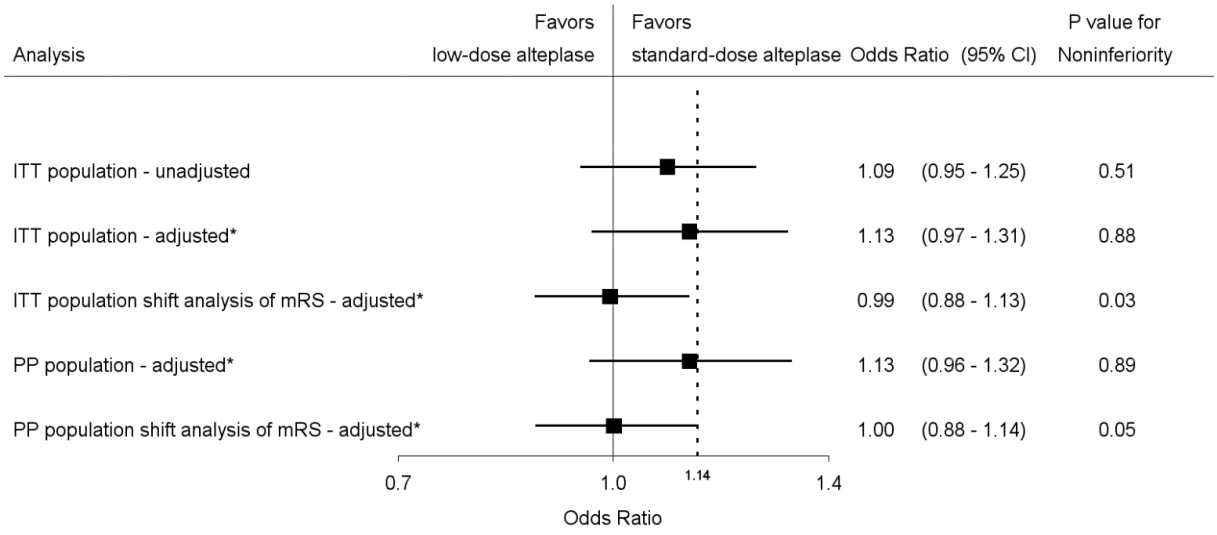


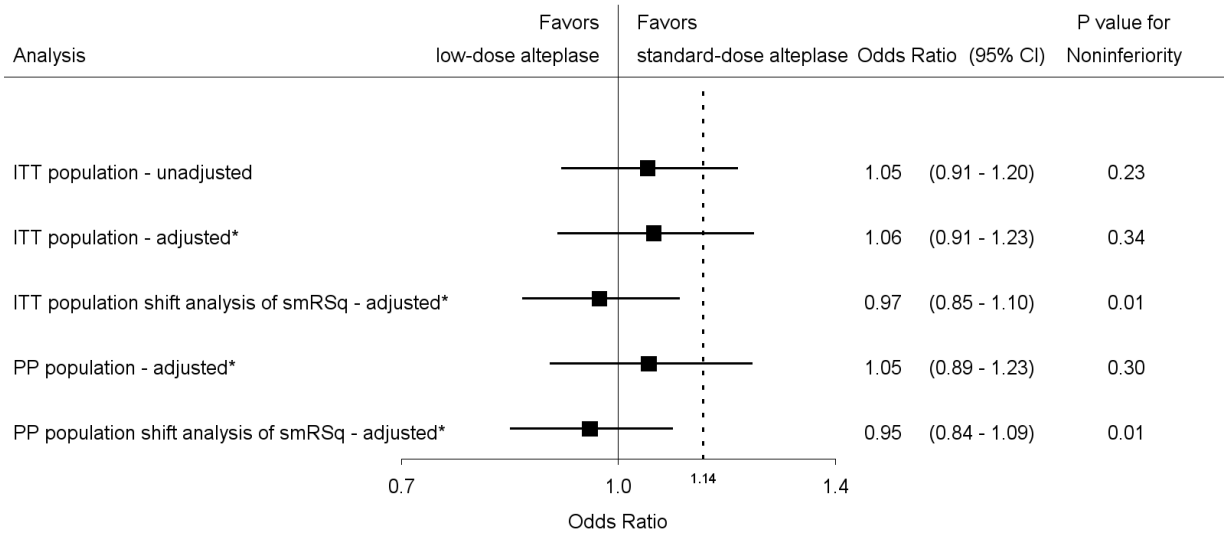
Figure S3. Comparative effects on the primary outcome by different analytical approaches



CI denotes confidence interval, ITT denotes intention to treat, mRS modified Rankin scale, PP per protocol. The primary outcome is death or disability defined by scores of 2 to 6 on the mRS. Scores on this scale range from 0 to 6, with higher scores indicating increased disability. The P value is for the comparison with the noninferiority margin of 1.14. The horizontal bars indicate 95% CI.

*adjustment for time from stroke onset to randomization, score as a continuous measure on the National Institutes of Health stroke scale (NIHSS), age, sex, ethnicity, pre-morbid score of 0 or 1 on the mRS, pre-morbid use of aspirin, other antiplatelet agent or warfarin, and any history of stroke, coronary artery disease, diabetes mellitus and atrial fibrillation.

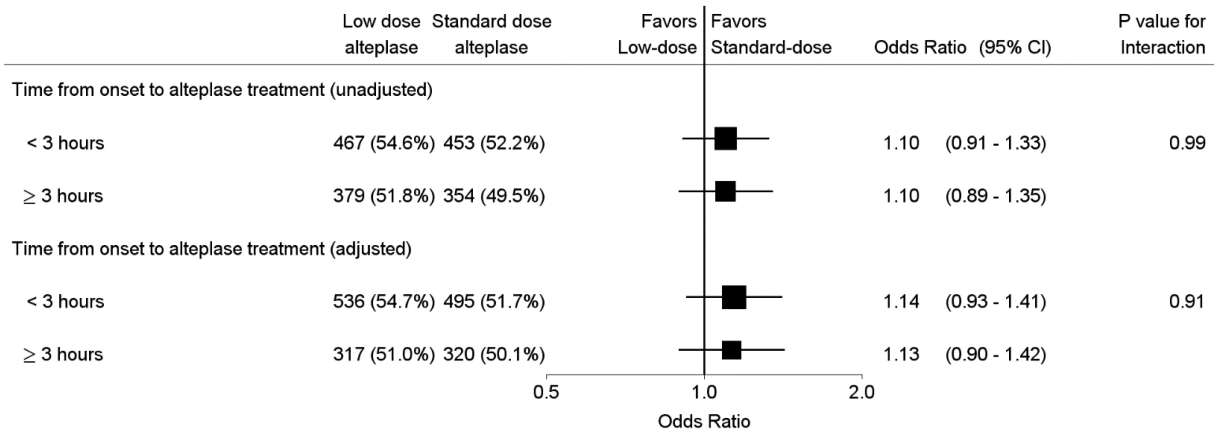
Figure S4. Post-hoc comparative effects on the primary outcome using the simplified modified Rankin scale questionnaire, by different analytical approaches



CI denotes confidence interval, ITT denotes intention to treat, smRSq simplified modified Rankin scale questionnaire, PP per protocol. The primary outcome is death or disability defined by scores of 2 to 6 on the mRS. Scores on this scale range from 0 to 6, with higher scores indicating increased disability. The P value is for the comparison with the noninferiority margin of 1.14. The horizontal bars indicate 95% CI.

*adjustment for time from stroke onset to randomization, score as a continuous measure on the National Institutes of Health stroke scale (NIHSS), age, sex, ethnicity, pre-morbid score of 0 or 1 on the mRS, pre-morbid use of aspirin, other antiplatelet agent or warfarin, and any history of stroke, coronary artery disease, diabetes mellitus and atrial fibrillation.

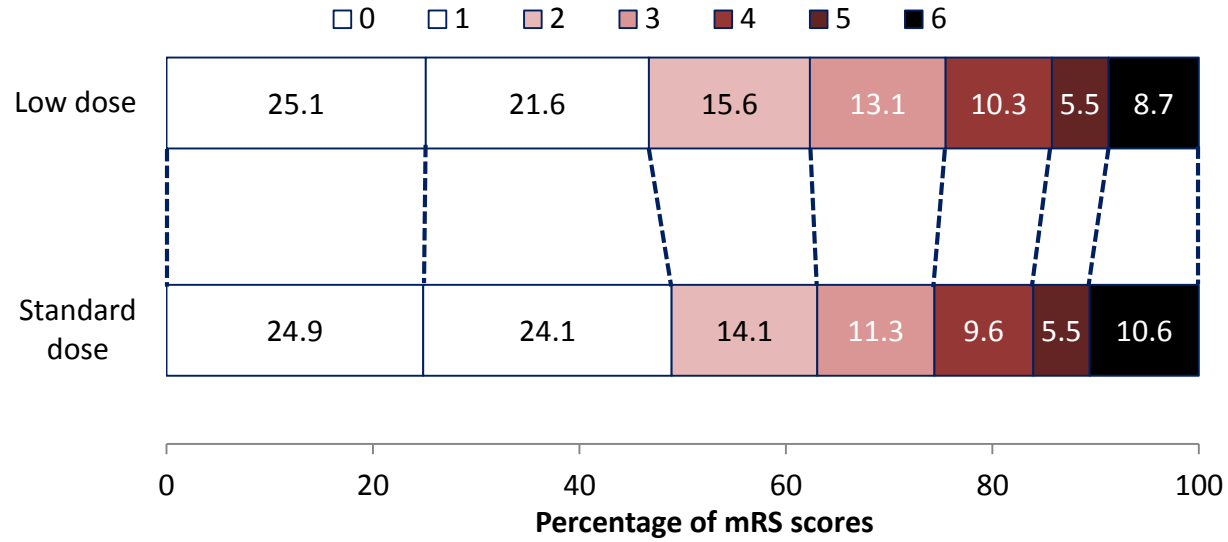
Figure S5. Comparative effects on the primary outcome by time (<3 vs. ≥3 hours) from stroke onset to start of alteplase



CI denotes confidence interval. The primary outcome is death or disability defined by scores of 2 to 6 on the modified Rankin scale (mRS). Scores on this scale range from 0 to 6, with higher scores indicating increased disability. The horizontal bars indicate 95% CI.

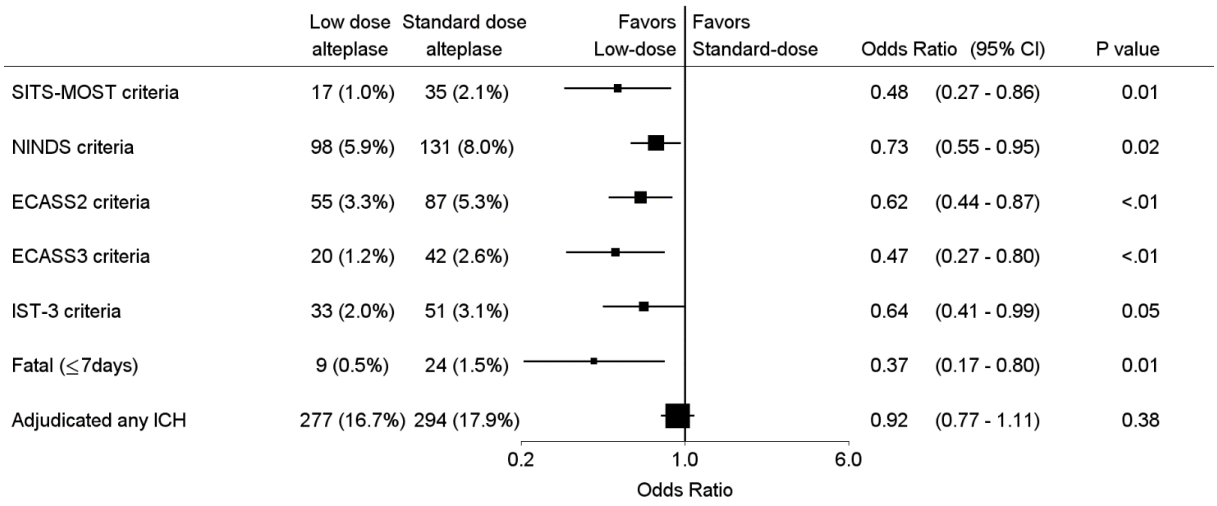
Adjustment for time from stroke onset to randomization, score as a continuous measure on the National Institutes of Health stroke scale (NIHSS), age, sex, ethnicity, pre-morbid score of 0 or 1 on the mRS, pre-morbid use of aspirin, other antiplatelet agent or warfarin, and any history of stroke, coronary artery disease, diabetes mellitus and atrial fibrillation.

Figure S6. Effects of low dose alteplase compared to standard dose alteplase on functional outcome according to an adjusted ordinal analysis of all categories of the modified Rankin scale (mRS) at 90 days, according to predefined covariates.*



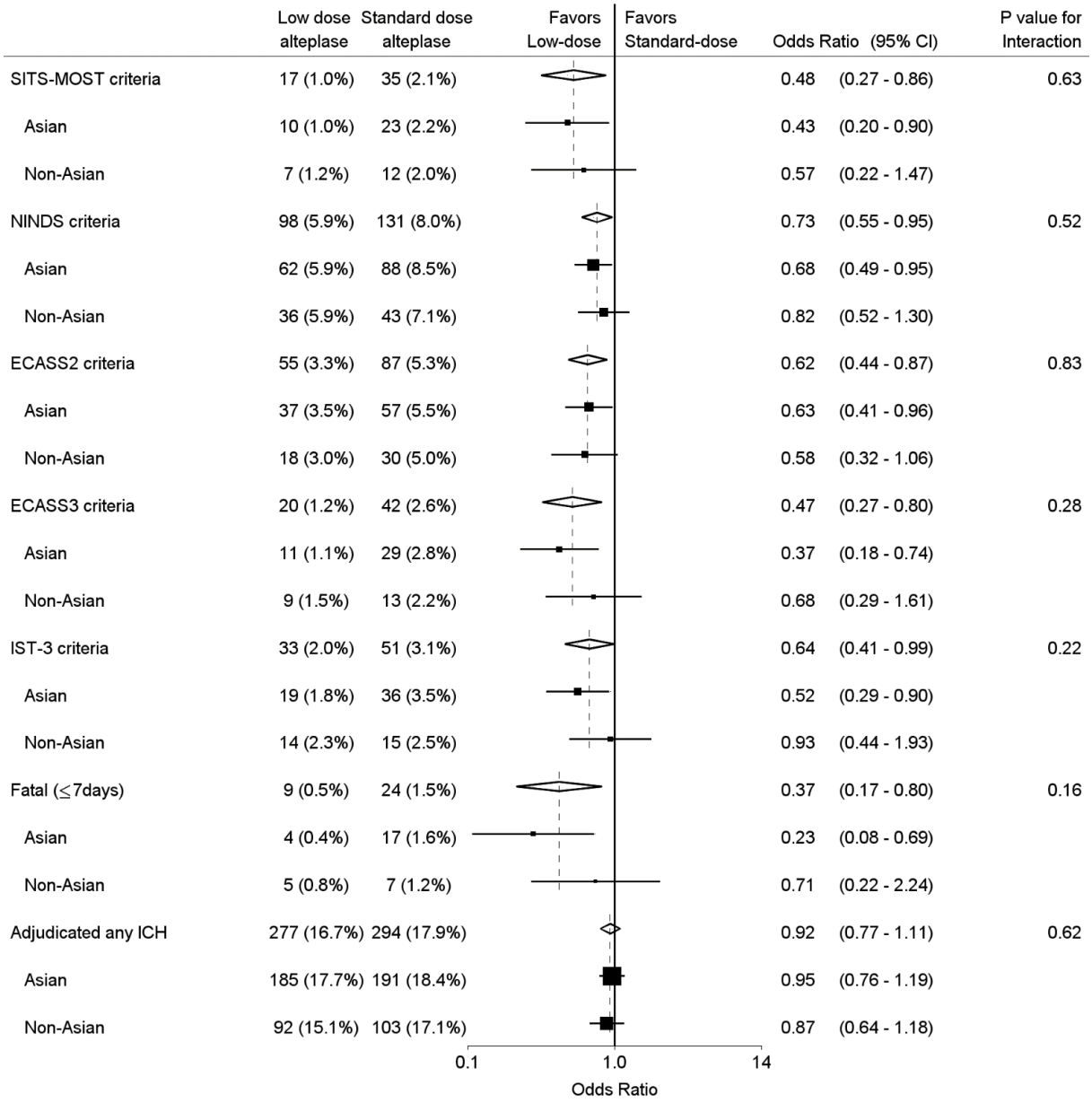
*The figure shows the distribution of scores on the mRS, where scores range from 0 to 6, with higher scores indicating increased disability. The common odds ratio for global function outcome was 0.99 (95% confidence interval 0.88 to 1.13; P=0.03 for noninferiority) after adjustment for site, time from stroke onset to randomization (<3 vs. ≥3 hours), score as a continuous measure on the National Institutes of Health stroke scale (NIHSS), age, sex, ethnicity, pre-morbid score of 0 or 1 on the mRS, pre-morbid use of aspirin, other antiplatelet agent or warfarin, and any history of stroke, coronary artery disease, diabetes mellitus and atrial fibrillation. There was a significant shift in the distribution of scores away from the noninferiority margin between patients in the low dose alteplase group and those in the standard dose alteplase group.

Figure S7. Effects of low dose alteplase compared to standard dose alteplase on different classifications of intracerebral hemorrhage *



*SITS-MOST denotes the Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NINDS, the National Institutes of Neurological Diseases and Stroke; ECASS, the European-Australian Cooperative Acute Stroke Study; IST-3, the third International Stroke Trial; ICH, intracerebral hemorrhage; CI, confidence interval. For categories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent 95% CIs.

Figure S8. Effects of low dose alteplase compared to standard dose alteplase on symptomatic intracerebral haemorrhage (ICH) by different criteria during 90 days of follow-up, in Asians versus non-Asians*



*Ethnicity defined by self-report. Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) is large local or remote parenchymal intracerebral hemorrhage (>30% of infarct affected by hemorrhage with mass effect or extension outside the infarct) with neurological deterioration (≥4 points increase on the National Institutes of Health stroke scale [NIHSS]) from baseline or death within 36 hours; the National Institutes of Neurological Diseases and Stroke (NINDS) trial criteria is any ICH with neurological deterioration (≥1 point on the NIHSS) from baseline or death within 36 hours; the second European-Australian Cooperative Acute Stroke Study (ECASS 2) of any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours; the ECASS 3 of any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours; the third International Stroke Trial (IST 3) of any either significant ICH (local or distant from the infarct) or significant hemorrhagic transformation of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment; and fatal ICH (parenchymal type 2) within 7 days of treatment; any ICH identified on the scan. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent 95% CIs.

Figure S9. Cumulative mortality curves for death by dose of alteplase

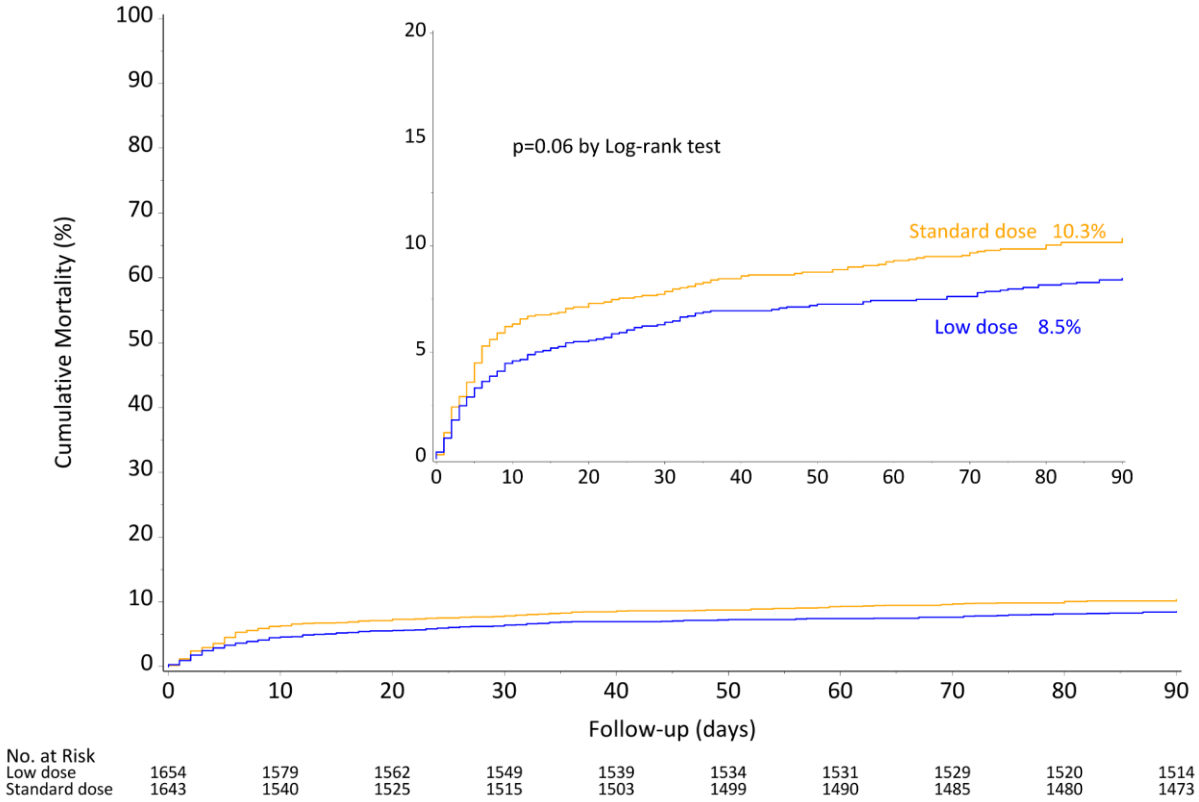
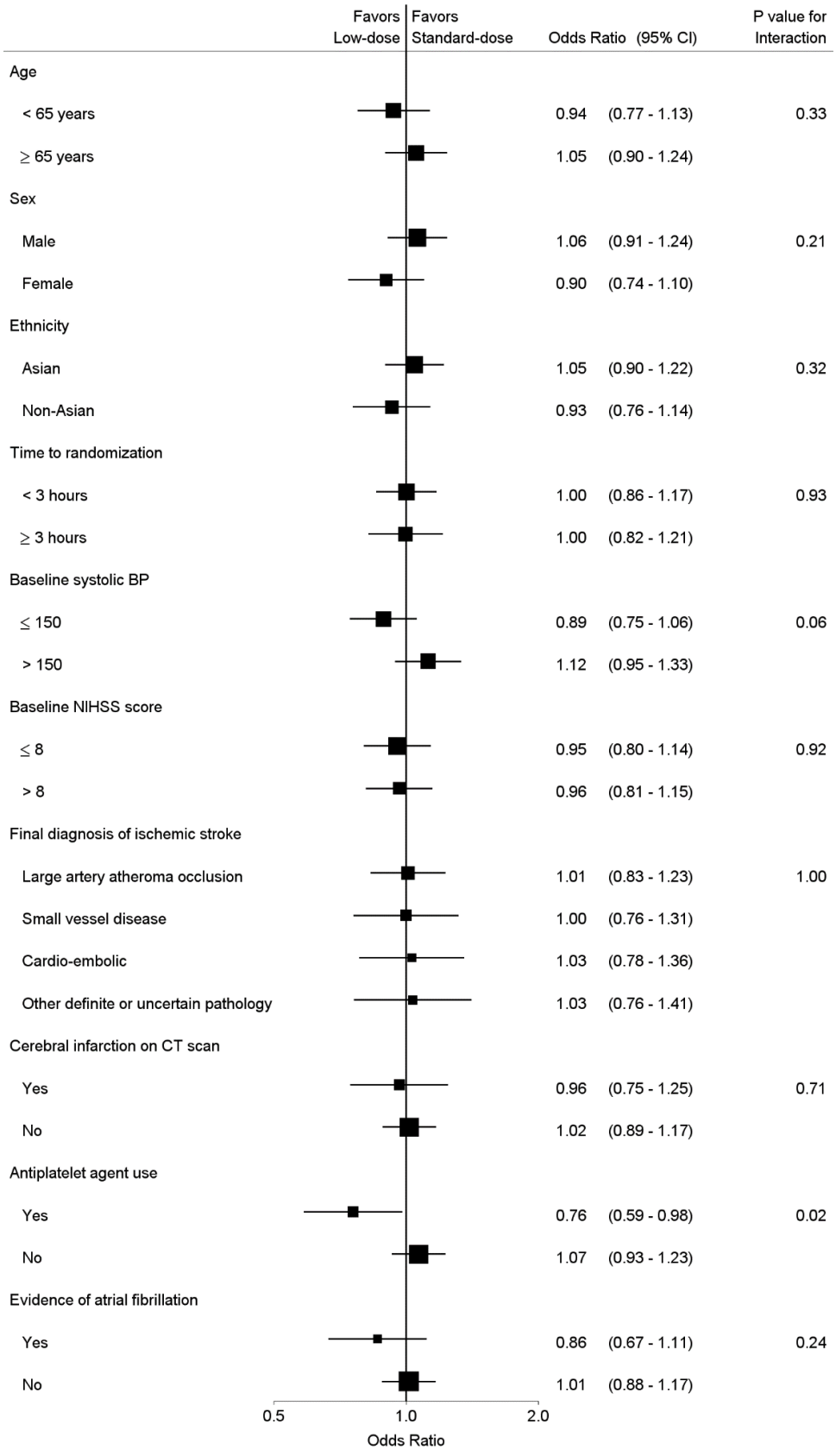
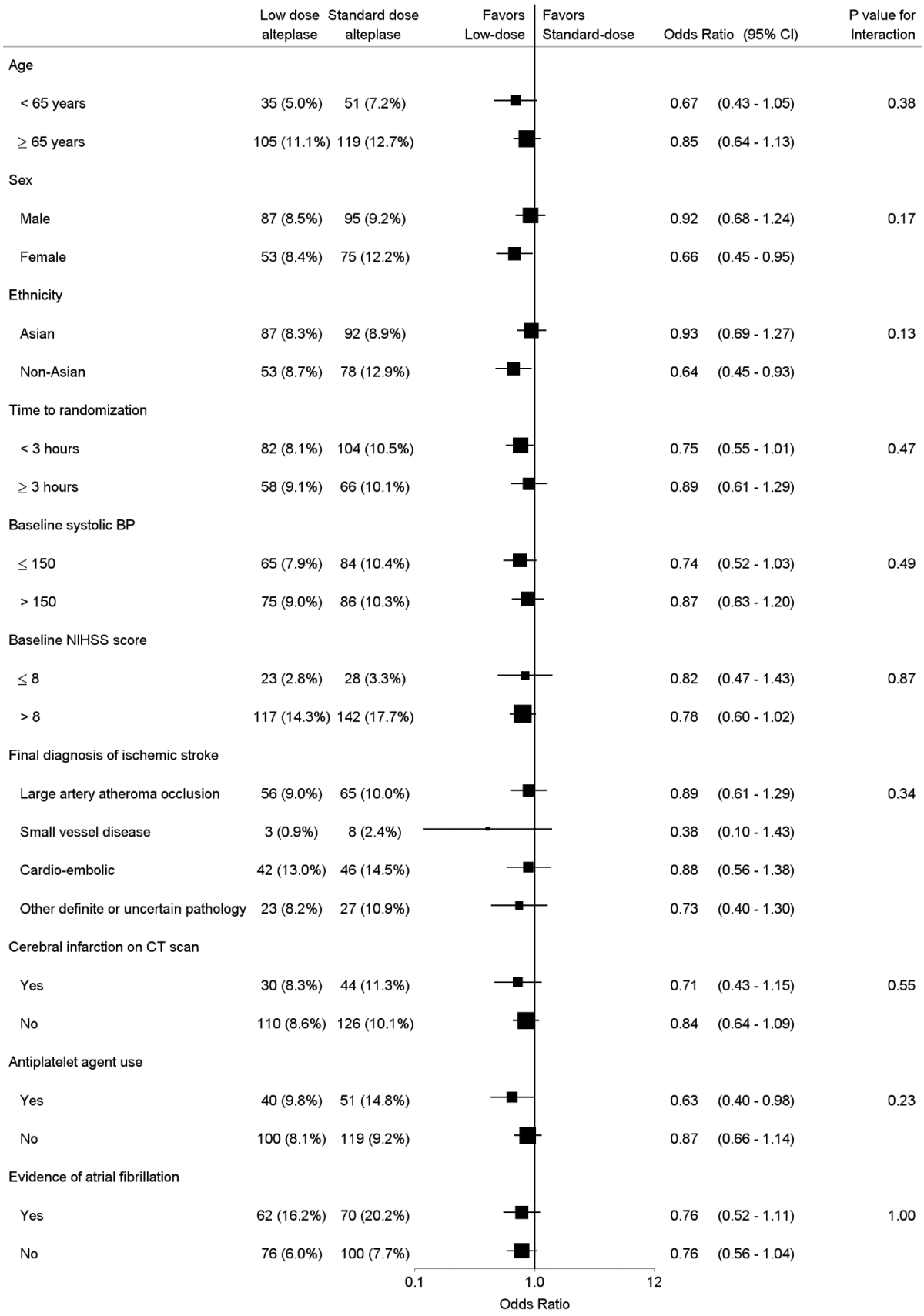


Figure S10. Effects of low dose alteplase compared to standard dose alteplase according to an unadjusted ordinal analysis of functional outcome across all categories on the modified Rankin scale at 90 days, according to predefined subgroups*



*BP denotes blood pressure, NIHSS National Institutes of Health stroke scale, CT computerized tomography, CI confidence interval. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent 95% CIs. For BP and NIHSS score, values are above and below median of distribution.

Figure S11. Effects of low dose alteplase compared to standard dose alteplase on death during 90 days of follow-up, according to predefined subgroups*



*BP denotes blood pressure, NIHSS National Institutes of Health stroke scale, CT computerized tomography, CI confidence interval. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent 95% CIs. For BP and NIHSS score, values are above and below median of distribution.

Figure S12. Relation of treatment effect by baseline National Institutes of Health Stroke Scale (NIHSS) score