Stable 1 Baseline characteristics according to functional outcome at 90 days

	mRS 0-1	mRS 2-6	P value
Age (years)	64.2 (12.6)	68.8 (12.6)	<0.0001
Female	526/1530 (34.4)	686/1667 (41.2)	<0.0001
Asian	1015/1530 (66.3)	1025/1667 (61.5)	0.004
Clinical features			
Systolic BP (mmHg)	148.7 (19.6)	149.9 (19.9)	0.091
Diastolic BP (mmHg)	84.5 (12.6)	84.9 (13.2)	0.396
NIHSS score	6.0 (4.0 - 10.0)	11.0 (7.0 - 17.0)	<0.0001
0-4	4892 (32.2)	154 (9.2)	
5-10	714 (46.7)	605 (36.3)	
11-15	202 (13.2)	427 (25.6)	
≥16	122 (8.0)	481(28.9)	
GCS score	15.0 (14.0 - 15.0)	15.0 (12.0 - 15.0)	<0.0001
Medical History			
Hypertension	924/1530 (60.4)	1087/1667 (65.2)	0.005
Previous stroke	247/1530 (16.1)	326/1667 (19.6)	0.012
Coronary artery disease	182/1530 (11.9)	293/1667 (17.6)	<0.0001
Other heart disease (valvular or other)	82/1530 (5.4)	148/1667 (8.9)	<0.0001
Atrial fibrillation	153/1530 (10.0)	305/1667 (18.3)	<0.0001
Diabetes mellitus	268/1530 (17.5)	357/1667 (21.4)	0.006
Hypercholesterolaemia	229/1530 (15.0)	307/1667 (18.4)	0.009
Current smoker	378/1530 (24.7)	366/1663 (22.0)	0.072
Pre-stroke function (mRS)			
No symptoms (mRS=0)	1354/1530 (88.5)	1250/1667 (75.0)	
No significant disability (mRS=1)	176/1530 (11.5)	417/1667 (25.0)	<0.0001
Medication at time of admission			
Antihypertensive agents	649/1530 (42.4)	802/1667 (48.1)	0.001
Warfarin anticoagulation	26/1528 (1.7)	51/1666 (3.1)	0.012
Aspirin or other anti-platelet agents	304/1528 (19.9)	426/1666 (25.6)	<0.0001
Glucose-lowering agents	168/1528 (11.0)	234/1666 (14.0)	0.009
Statin or other lipid lowering agent	260/1527 (17.0)	333/1666 (20.0)	0.032
Randomised to low-dose alteplase treatment	748/1530 (48.9)	851/1667 (51.0)	0.222
Time from stroke onset to randomisation	2.7 (2.0 - 3.5)	2.7 (2.0 - 3.5)	0.281

Data are n (%), mean (SD), or median (IQR)· The P values from the univariate analysis are based on Chi-square, T test, or Wilcoxon signed-rank test

BP: blood pressure; NIHSS: The National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; mRS: modified Rankin scale, SE: standard error

Stable 2: Baseline characteristics by sICH according to SITS-MOST diagnostic criteria

	No sICH	sICH	P value
Age (years)	66.5 (12.8)	68.9 (10.7)	0.198
Female	1198/3146 (38.1)	14/ 51 (27.5)	0.121
Asian	2007/3146 (63.8)	33/ 51 (64.7)	0.893
Clinical features			
Systolic BP (mmHg)	149.2 (19.8)	156.0 (16.9)	0.015
Diastolic BP (mmHg)	84.6 (12.9)	90.8 (13.0)	0.001
NIHSS score	8.0 (5.0 - 14.0)	12.0 (7.0 - 17.0)	0.011
GCS score	15.0 (14.0 - 15.0)	14.0 (13.0 - 15.0)	0.027
Medical History			
Hypertension	1975/3146 (62.8)	36/ 51 (70.6)	0.252
Previous stroke	561/3146 (17.8)	12/ 51 (23.5)	0.293
Atrial fibrillation	440/3146 (14.0)	18/ 51 (35.3)	<0.000
Diabetes mellitus	617/3146 (19.6)	8/ 51 (15.7)	0.483
Hypercholesterolaemia	531/3146 (16.9)	5/ 51 (9.8)	0.180
Current smoker	734/3142 (23.4)	10/ 51 (19.6)	0.529
Pre-stroke function (mRS)			
No symptoms (mRS=0)	2565/3146 (81.5)	39/ 51 (76.5)	0.356
No significant disability (mRS=1)	581/3146 (18.5)	12/ 51 (23.5)	
Medication at time of admission			
Antihypertensive agents	1429/3146 (45.4)	22/ 51 (43.1)	0.745
Warfarin anticoagulation	75/3143 (2.4)	2/ 51 (3.9)	0.478
Aspirin or other anti-platelet agents	711/3143 (22.6)	19/ 51 (37.3)	0.014
Glucose-lowering agents	398/3143 (12.7)	4/ 51 (7.8)	0.303
Statin or other lipid lowering agent	586/3142 (18.7)	7/ 51 (13.7)	0.370
Randomised to low-dose alteplase treatment	1429/3146 (45.4)	22/ 51 (43.1)	0.745
Time from stroke onset to randomisation	2.7 (2.0 - 3.5)	2.7 (2.2 - 3.3)	0.9111

Data are n (%), mean (SD), or median (IQR)· The P values are based on Chi-square, T test, or Wilcoxon signed-rank test

NIHSS: The National Institutes of Health Stroke Scale; BP: blood pressure; GCS: Glasgow Coma Scale; mRS: modified Rankin scale

STable 3 Patient characteristics by net advantage from low-dose alteplase

20% weight to benefit	**Development cohort**		**Validation cohort**	
	No (n=2025, 63%)	**Yes (n=1172, 37%)**	**No (n=1067, 70%)**	**Yes (n=458, 30%)**
Age, years	68.5 (12.5)	63.3 (12.7)	70 (12)	65 (13)
Systolic BP, mmHg	158 (17)	134 (14)	156 (28)	129 (16)
NIHSS	8 (4-15)	8 (6-12)	11 (6-17)	9 (6-14)
Pre-stroke mRS=0	1599 (78.9%)	1005 (85.8%)	857 (80%)	423 (92.4%)
Atrial fibrillation	623 (30.8%)	1 (0.1%)	618 (57.9%)	6 (1.3%)
Diabetes mellitus	405 (20.0%)	220 (18.8%)	276 (25.9%)	95 (20.7%)
30% weight to benefit	**No (n=888, 28%)**	**Yes (n=2309, 72%)**	**No (n=775, 50.8%)**	**Yes (n=750, 49.2%)**
Age, years	71 (12)	64 (13)	71 (11)	65 (13)
Systolic BP, mmHg	157 (19)	146 (19)	158 (29)	137 (21)
NIHSS	12 (6-18)	8 (5-12)	14 (8-18)	8 (5-14)
Pre-stroke mRS=0	639 (72%)	1965 (85.1%)	597 (77%)	683 (91.1%)
Atrial fibrillation	585 (65.9%)	39 (1.7%)	572 (73.8%)	52 (6.9%)
Diabetes mellitus	177 (19.9%)	448 (19.4%)	201 (25.9%)	170 (22.7%)
40% weight to benefit	**No (n=496, 15%)**	**Yes (n=2701, 85%)**	**No (n=, %)**	**Yes (n=, %)**
Age, years	74 (11)	65 (13)	73 (10)	66 (13)
Systolic BP, mmHg	156 (16)	148 (20)	161 (28)	140 (24)
NIHSS	15 (9-19)	8 (5-12)	15 (9-19)	9 (5-14)
Pre-stroke mRS=0	322 (64.9%)	2282 (84.5%)	419 (74.6%)	861 (89.4%)
Atrial fibrillation	462 (93.2%)	162 (6%)	464 (82.6%)	160 (16.6%)
Diabetes mellitus	105 (21.2%)	520 (19.3%)	151 (26.9%)	220 (22.9%)
60% weight to benefit	**No (n=166, 5%)**	**Yes (n=3031, 95%)**	**No (n=219, 14.4%)**	**Yes (n=1306, 85.6%)**
Age, years	79 (9)	66 (13)	77 (10)	67 (12)
Systolic BP, mmHg	163 (13)	149 (20)	168 (29)	144 (26)
NIHSS	13 (9-17)	8 (5-13)	17 (13-20)	9 (6-15)
Pre-stroke mRS=0	87 (52.4%)	2517 (83%)	111 (50.7%)	1169 (89.5%)
Atrial fibrillation	166 (100%)	458 (15.1%)	193 (88.1%)	431 (33%)
Diabetes mellitus	38 (22.9%)	587 (19.4%)	71 (32.4%)	300 (23.0%)
70% weight to benefit	**No (n=64, 2%)**	**Yes (n=3133, 98%)**	**No (n=129, 8.5%)**	**Yes (n=1396, 91.5%)**
Age, years	81 (9)	66 (13)	79 (8)	67 (12)
Systolic BP, mmHg	167 (11)	149 (20)	169 (30)	146 (26)
NIHSS	18 (16-22)	8 (5-13)	18 (15-21)	10 (6-15)
Pre-stroke mRS=0	18 (28.1%)	2586 (82.5%)	42 (32.6%)	1238 (88.7%)
Atrial fibrillation	64 (100%)	560 (17.9%)	114 (88.4%)	510 (36.5%)
Diabetes mellitus	11 (17.2%)	614 (19.6%)	49 (38%)	322 (23.1%)
80% weight to benefit	**No (n=15, 0.5%)**	**Yes (n=3182, 99.5%)**	**No (n=79, 5.2%)**	**Yes (n=1446, 94.8%)**
Age, years	87 (6)	66 (13)	80 (8)	68 (12)
Systolic BP, mmHg	172 (8)	149 (20)	163 (30)	147 (27)
NIHSS	17 (16-20)	8 (5-14)	19 (16-22)	10 (6-16)
Pre-stroke mRS=0	0 (0%)	2604 (81.8.%)	13 (16.5%)	1267 (87.6%)
Atrial fibrillation	15 (100%)	609 (19.1%)	72 (91.1%)	552 (38.2%)
Diabetes mellitus	3 (20.0%)	622 (19.6%)	33 (41.8%)	338 (23.4%)

BP: blood pressure; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke Scale

SFigure I Benefit and risk calculation equations

Net advantage = WB_i / $(1-W)R_i$

(A) Excess benefit from low-dose alteplase: $B_i = B_i^L - B_i^S$

$B_i^L = \frac{1}{1+\exp(A)}$,

where A = 3.1274-0.0117*age-0.00598*SBP-0.9667*(if baseline NIHSS 5-10)-1.9048*(if baseline NIHSS 11-15)-2.4569*(if baseline NIHSS ≥16) -0.7921*(if pre-stroke mRS≥1)+1.3955*(if atrial fibrillation at baseline)-0.2604*(if diabetes mellitus at baseline)-0.1443*1-0.0238*(if atrial fibrillation at baseline)*age

$B_i^S = \frac{1}{1+\exp(A)}$,

where A = 3.1274-0.0117*age-0.00598*SBP-0.9667*(if baseline NIHSS 5-10)-1.9048*(if baseline NIHSS 11-15)-2.4569*(if baseline NIHSS ≥16) -0.7921*(if pre-stroke mRS≥1)+1.3955*(if atrial fibrillation at baseline)-0.2604*(if diabetes mellitus at baseline)-0.1443*0-0.0238*(if atrial fibrillation at baseline)*age

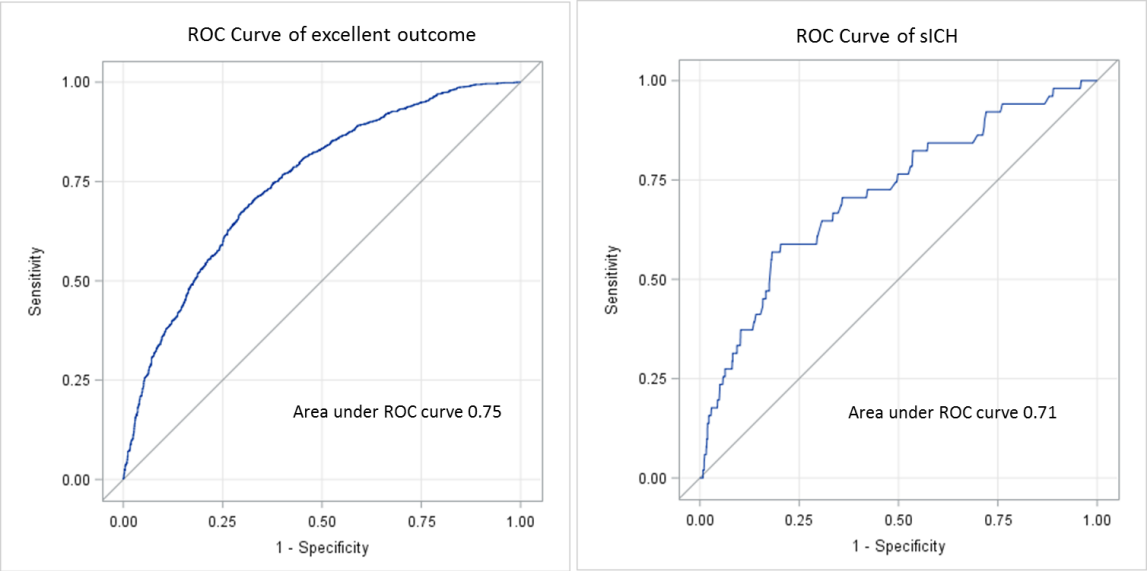
(B) Excess risk from low-dose alteplase: $R_i = R_i^L - R_i^S$

$R_i^L = \frac{1}{1+\exp(A)}$,

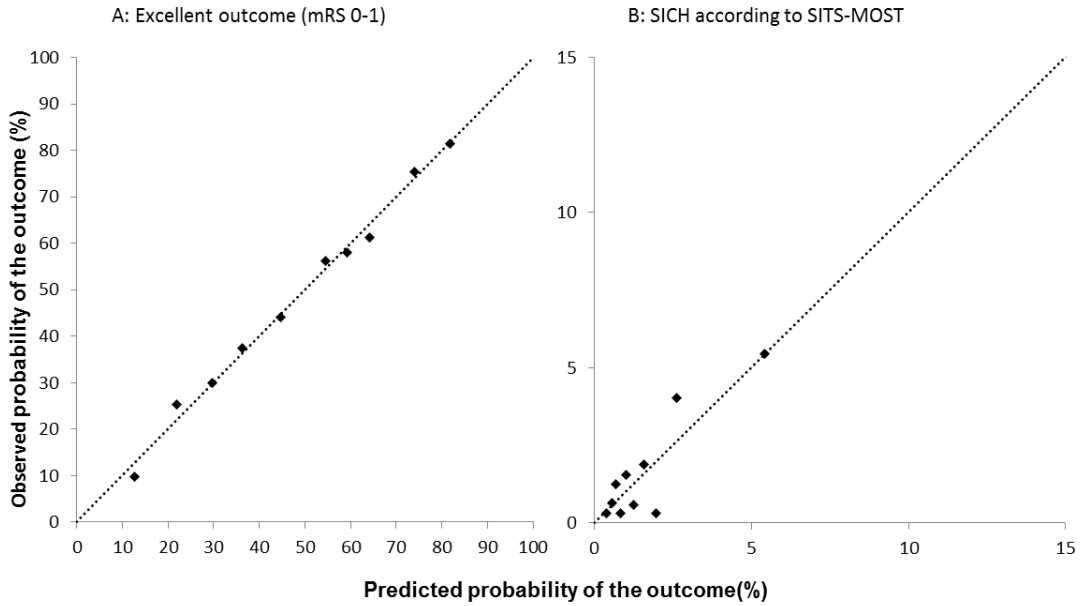
where A = -7.3599+0.0206*SBP+1.3316*(if atrial fibrillation at baseline)-0.8014*1

$R_i^S = \frac{1}{1+\exp(A)}$,

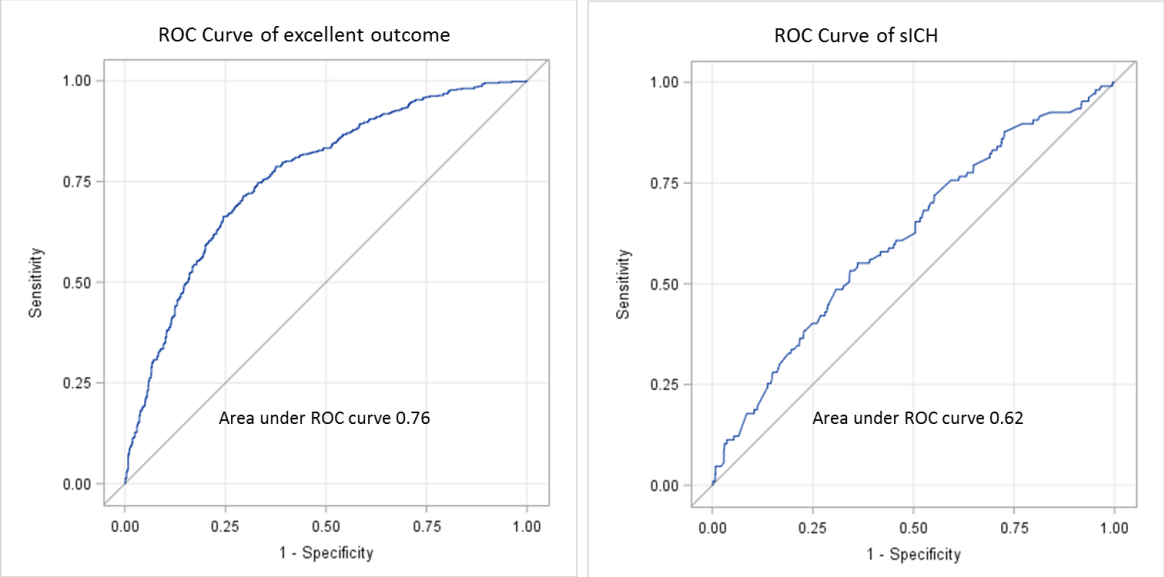
where A = -7.3599+0.0206*SBP+1.3316*(if atrial fibrillation at baseline)-0.8014*0



SFigure II Receiver-operating characteristic (ROC) curves of development model



SFigure III Predicted vs. observed probabilities of outcomes in the development model



SFigure IV Receiver-operating characteristic (ROC) curves of validation model