SUPPLEMENTAL MATERIAL

Targeting rtPA in acute ischemic stroke based on risk of intracranial hemorrhage or poor functional outcome: an analysis of the IST-3 trial

Authorship statement

WW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Whiteley, Thompson, Wardlaw, Cohen, Lindley, Murray, Sandercock

Acquisition of data: Whiteley, Wardlaw, Lindley, Sandercock

Analysis and interpretation of data: Whiteley, Thompson, Wardlaw, Cohen, Lindley, Murray, Sandercock

Drafting of the manuscript: Whiteley, Thompson

Critical revision of the manuscript for important intellectual content: Wardlaw, Cohen, Lindley, Murray, Sandercock

Statistical analysis: Thompson, Whiteley, Cohen, Murray

Obtained funding: Sandercock, Lindley, Wardlaw

Study supervision: Whiteley, Wardlaw, Murray, Sandercock

Systematic search for relevant models.

We searched the medical literature from inception to 25th January 2013 for studies which had developed multivariate models for the prediction of intracranial hemorrhage or poor functional outcome after treatment of acute ischemic stroke patients with rtPA. Models were eligible for inclusion if they were developed with a cohort of acute ischemic stroke patients, all of whom had been treated with rtPA, and reported a prediction model either as a score, or a model with constant and weighting for each of the covariates.

We identified studies with an electronic search strategy, reference lists of relevant studies, forward searches from relevant studies with Google Scholar and from our own files. We reviewed titles and abstracts of potentially relevant studies, and extracted models in duplicate from relevant studies.

The literature search identified 797 publications. Of these, 11 studies were relevant, which reported the development of 12 models.

Medline electronic search strategy

1 Cerebrovascular disorders/
2 exp Brain ischemia/
3 Carotid artery diseases/ or Carotid artery thrombosis/
4 stroke/ or exp brain infarction/
5 exp Hypoxia-ischemia, brain/
6 Cerebral arterial diseases/ or Intracranial arterial diseases/
7 exp "Intracranial embolism and thrombosis"/
8 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch?emic attack$ or tia$).tw.
9 (brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
11 9 and 10
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
13 Thrombolytic therapy/
14 Fibrinolysis/
15 exp plasminogen activators/
16 Fibrinolytic agents/ or Plasmin/ or Plasminogen/
17 (thromboly$ or fibrinoly$ or clot lysis).tw.
18 (plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).tw.
19 (alteplase).tw.
20 exp "intracranial embolism and thrombosis"/dt or Thromboembolism/dt
21 Thrombosis/dt [Drug Therapy]
22 or/13-21
23 12 and 22
24 randomized controlled trial.pt.
25 randomized controlled trials/
26 controlled clinical trial.pt.
27 controlled clinical trials/
28 random allocation/
29 double-blind method/
30 single-blind method/
31 single-blind method/
32 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
33 placebos/
34 placebo$.tw.
35 random$.tw.
36 research design/
37 clinical trial phase ii.pt.
38 clinical trial phase iii.pt.
39 clinical trial phase iv.pt.
40 multicenter study.pt.

41 intervention studies/
42 control$.tw.
43 latin square.tw.
44 "comparative study"/
45 exp evaluation studies/
46 Follow-up studies/
47 Prospective studies/
48 prospective.tw.
49 (versus or allocat$).tw.
50 experimental group$.tw.
51 cerebral hemorrhage/chemically induced*
52 ROC curve/
53 Prognosis/
54 Predictive value of tests/
55 Area under curve/
56 Logistic models/
57 or/24-50
58 or/52-56
59 23 and 51 and 57 and 58
60 limit 59 to human

Scores identified by systematic review not assessed in the analysis

Cucchiara B, Kasner SE, Tanne D, Levine SR, Demchuk A, Messe SR, Sansing L, Lees KR, Lyden P, SAINT I Factors associated with intracerebral hemorrhage after thrombolytic therapy for ischemic stroke: pooled analysis of placebo data from the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II Trials. Stroke 2009;40: 3067-3072.

Saposnik G, Fang J, Kapral MK, Tu JV, Mamdani M, Austin P, Johnston SC The iScore Predicts Effectiveness of Thrombolytic Therapy for Acute Ischemic Stroke. Stroke 2012; 43: 1315-1322.

Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249-56

NINDS rt-PA Stroke Study Group. Intracerebral Hemorrhage After Intravenous t-PA Therapy for Ischemic Stroke. Stroke 1997;28:2109-18.

Supplementary table I Results of a systematic literature search for models applicable to the IST-3 dataset.

	Models to predict post rtPA ICH										Models to predict post rtPA poor outcome					
	HAT[1]		SEDAN[2]		SITS[3]		GRASPS[4]		SPAN-100[5]		Stroke tPI[6]		DRAGON[7]		THRIVE[8]	
Outcome	sICH >4 NIHSS		sICH		SITS sICH		NINDS sICH		NINDS sICH		mRS 5 or dead		mRS 5 or dead		mRS 3-6	
NIHS score	<15	0	0-9	0	<7	0	<5	25	Total		Per point	0.125	<5	0	≤10	0
	15-19	1	≥10	1	7-12	1	6-10	27	score				5-9	1	11-20	2
	≥20	2			≥13	2	11-15	34					10-15	2	≥21	4
							16-20	40					>15	3		
							>20	42								
Glucose level (mg/dl)	>200 or DM	1	<144	0	<180	0	<100	2			Per mg/dl	0.077	≥144	1	No DM	0
			144-216	1	≥180	2	100-149	6							Yes DM	1
			>216	2			≥150	8								
Age			<75	0	<72	0	≤60	8	Total		Per year	0.057	<65	0	<60	0
			≥75	1	≥72	1	61-70	11	age				65-79	1	60-79	1
							71-80	15					≥80	2	≥80	2
							>80	17								
CT appearance of infarct	None	0	None	0							Per ASPECTS	-0.171				
	<1/3 MCA	1	Yes	1									None	0		
	≥1/3 MCA	2											Either	1		
													Both	2		
CT Hyper dense artery			None	0												
			Yes	1												
Systolic blood pressure (mmHg)					≤145	0	<120	10								
					>145	1	120-149	14								
							150-179	18								
							≥180	21								
Prior hypertension					None	0									None	0
					Yes	1									Yes	1
Use of antiplatelets					Aspirin	2										
					+ clopidogrel	3										
Weight (kg)					<95	0										
					≥95	1										
Delay to rtPA (mins)					<180	0							≤90	0		
					≥180	1							>90	1		
Sex							Male	4								
Ethnicity							Asian	9								
Prior disability													Prestroke mRS>1	1		
AUROCC in development	0.68 (0.56-0.81)				0.71		0.71 (0.68-0.73)				0.78 (0.77 -0.79)		0.84 (0.80-0.87)			
AUROCC in external test	0.88 (0.77-0.99)[1]		0.77(0.71-0.83)		0.69		0.70 (0.67-0.74)				0.76(0.75-0.78)[9]		0.80 (0.74-0.86)			
AUROCC in external test	0.72 (0.58–0.86)[10]										0.78[11]					

AUROCC: area under receiver operating characteristic curve ; DM: diabetes mellitus; DRAGON: Dense artery, Rankin score, Age, Glucose, Onset to treatment time, NIHSS score; GRASPS: Glucose Race Age Sex Pressure Stroke Severity score; mRS: modified Rankin score; HAT: haemorrhage after thrombolysis score; NIHSS: National Institutes of Health Stroke Scale; NINDS: National Institutes of Neurological Disorders and Stroke; OR: odds ratio; sICH: symptomatic intracranial haemorrhage; SITS: Safe Implementation of Treatments in Stroke; SPAN: Stroke prognostication using age and NIHSS; THRIVE: Totalled Health Risk in Vascular Events

SUPPLEMENTARY TABLE I REFERENCES

(1) Lou M, Safdar A, Mehdiratta M, Kumar S, Schlaug G, Caplan L et al. The HAT Score. *Neurology* 2008;71:1417-23.

(2) Strbian D, Engelter S, Michel P, Meretoja A, Sekoranja L, Ahlhelm FJ et al. Symptomatic intracranial hemorrhage after stroke thrombolysis: The SEDAN Score. *Ann Neurol* 2012;71:634-41.

(3) Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D et al. Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated With Intravenous Alteplase. *Stroke* 2012;43:1524-31.

(4) Menon BK, Saver JL, Prabhakaran S, Reeves M, Liang L, Olson DM et al. Risk Score for Intracranial Hemorrhage in Patients With Acute Ischemic Stroke Treated With Intravenous Tissue-Type Plasminogen Activator. *Stroke* 2012;43:2293-9.

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(6) Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The Stroke Thrombolytic Predictive Instrument: A Predictive Instrument for Intravenous Thrombolysis in Acute Ischemic Stroke. *Stroke* 2006;37:2957-62.

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(8) Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting Long-Term Outcome after Endovascular Stroke Treatment: The Totaled Health Risks in Vascular Events Score. *American Journal of Neuroradiology* 2010;31:1192-6.

(9) Uyttenboogaart M, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Utility of the stroke-thrombolytic predictive instrument. *Journal of Neurology, Neurosurgery & Psychiatry* 2008;79:1079-81.

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(11) McMeekin P, Flynn D, Ford GA, Rodgers H, Thomson RG. Validating the Stroke-Thrombolytic Predictive Instrument in a Population in the United Kingdom. *Stroke* 2012;43:3378-81.

Supplementary table II Prediction model for symptomatic ICH in patients treated with rtPA in IST-3. AUROCC=0.65 after correction for optimism (N=1,361).

Variable	Adjusted odds ratio	95% CI	β-coefficient (SE)
Age (years)	1.00	0.98 to 1.02	0.0004 (0.0096)
NIHSS	1.05	1.02 to 1.08	0.0456 (0.0144)
Glucose (mg/dl)	1.00	1.00 to 1.01	0.0040 (0.0021)
Prior Hypertension	0.96	0.65 to 1.41	-0.0418 (0.1964)
Atrial Fibrillation	0.74	0.50 to 1.09	-0.3061 (0.2007)
Visible infarct on CT	1.20	0.83 to 1.75	0.1861 (0.1907)
Anti-platelet	1.62	1.12 to 2.37	0.4853 (0.1917)
Diabetes	1.07	0.67 to 1.70	0.0645 (0.2367)
Leukoaraiosis	1.16	0.79 to 1.69	0.1465 (0.1935)
Intercept	-	-	-4.2071 (0.7977)

Supplementary table III. Metrics of model performance when predicting sICH outcome defined as 'parenchymal haemorrhage' by each of the nine models identified through systematic review and the model developed in rt-PA treated IST3 patients.

Model	Score	n/N	R^2	AUROCC	AUROCC 95% CI	Calibration	
			(%)			Intercept	Slope
HAT	0 to 5	116/1365	3.70	0.63	0.58 to 0.69	0.08	0.40
SEDAN	0 to 7	116/1365	4.02	0.63	0.58 to 0.68	-0.14	0.54
SITS	0 to 11	114/1357	2.84	0.60	0.55 to 0.65	1.31	0.61
GRASPS	45 to 101	116/1365	3.21	0.63	0.58 to 0.68	0.60	0.62
SPAN-100[1]	0 to 1	133/1507	1.10	0.56	0.51 to 0.60	-1.04	0.32
STROKE TPI	GLM	116/1365	3.97	0.64	0.59 to 0.69	-1.37	0.34
DRAGON	0 to 10	116/1363	5.18	0.66	0.61 to 0.70	-3.35	0.49
THRIVE	0 to 9	132/1504	2.63	0.62	0.57 to 0.67	-3.21	0.37
NIHSS/age	GLM	133/1507	3.96	0.64	0.59 to 0.69	-4.11	0.29
IST3 model	GLM	115/1361	5.37	0.66	0.61 to 0.71	0.33	1.11