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Clinical imaging factors of excellent outcome after thrombolysis in large-vessel stroke: a THRACE subgroup analysis

Nolwenn Riou-Comte,[1] Benjamin Gory,[2] Marc Soudant ,[3] François Zhu,[2] Yu Xie,[2] Lisa Humbertjean,[1] Gioia Mione,[1] Catherine Oppenheim,[4] Francis Guillemin,[3] Serge Bracard,[2] Sébastien Richard ,[1] on behalf of the THRACE investigators

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[1]Department of Neurology-Stroke Unit, CIC-P 1433, INSERMU1116, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France
[2]Department of Diagnostic and Therapeutic Neuroradiology, INSERM U1254, IADI, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France
[3]Clinical Investigation Centre-Clinical Epidemiology 1433, INSERM, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France
[4]Department of Neuroradiology, INSERM U894, Université Paris-Descartes, Sainte-Anne Hospital, Paris, France

Correspondence to
Professor Sébastien Richard; s.richard@chru-nancy.fr

ABSTRACT

Background For patients with stroke with large-vessel occlusion (LVO), study of factors predicting response to intravenous thrombolysis (IVT) would allow identifying subgroups with high expected gain, and those for whom it could be considered as futile, and even detrimental. From patients included in the Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke trial, we investigated clinical-imaging factors associated with optimal response to IVT.

Methods We included patients receiving IVT alone. Excellent outcome was defined by a 3-month modified Rankin Scale (mRS) score ≤1. Clinical-imaging predictors were assessed on multivariate analysis after multiple imputations. The predictive performance of the model was assessed with the C-statistic.

Results Among 247 patients with LVO treated with IVT alone, 77 (31%) showed 3-month mRS ≤1. Predictors of 3-month mRS ≤1 were no medical history of hypertension (OR 2.43; 95% CI 1.74 to 3.38; p=0.007); no current smoking (OR 2.76; 95% CI 1.79 to 4.26; p=0.02); onset-to-IVT time (OR 0.47 per hour increase; 95% CI 0.23 to 0.78; p=0.003); diffusion-weighted imaging (DWI) volume (OR 0.78 per 10 mL increase; 95% CI 0.68 to 0.89; p=0.0004); presence of susceptibility vessel sign (SVS) (OR 7.89; 95% CI 1.65 to 37.78; p=0.01) and SVS length (OR 0.87 per mm increase; 95% CI 0.80 to 0.94; p=0.001). The prediction models showed a C-statistic=0.79 (95% CI 0.79 to 0.80).

Conclusions In patients with stroke with anterior-circulation LVO treated with IVT alone, predictors of excellent outcome at 3 months were no medical history of hypertension or current smoking, reduced onset-to-IVT time, small DWI volume, presence of SVS and short SVS length. These predictive factors could help practitioners in decision-making for IVT implementation in reperfusion strategies, all the more for the drip and ship paradigm.

Trial registration number NCT01062698.

INTRODUCTION

Intravenous thrombolysis (IVT) is a cornerstone in therapeutic strategies for cerebral reperfusion. It allows for early reperfusion in about one-third of patients with acute ischaemic stroke due to large-vessel occlusion (LVO) of anterior circulation.[1] While mechanical thrombectomy (MT) is mostly performed in comprehensive stroke centres with endovascular capacities, patients may have wide access to IVT treatment in developed stroke networks. Main indications and contraindications have been defined following original studies assessing IVT gain and safety.[2 3] Nowadays, both are debated in practice as well as in clinical research.[4] Then, identification of factors predicting optimal response to IVT or not, would help to define subgroups of patients with LVO for whom high gain is expected or, on the contrary, those with an overriding haemorrhagic risk.

Most studies have explored the association between isolated imaging criteria or clinical findings and response to IVT.[5 6] Most prediction models for stroke outcome were developed without considering a revascularisation strategy and without identifying patients with LVO as a poor prognosis subgroup.[7]

From the major trial Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke (THRACE),[8] we sought to determine the clinical and imaging predictors of 3-month excellent outcome after IVT alone in patients with anterior-circulation LVO and to evaluate the predictive performance of early neurological improvement to anticipate this successful response to treatment.

METHODS

Study population

The study was a subgroup analysis of the randomised controlled THRACE trial study.[8] Patients with LVO of the anterior circulation treated with IVT only were included in the present analysis.

Outcome

The primary end point was 3-month excellent outcome after IVT alone, defined as a modified Rankin Scale (mRS) score 0–1 at 3 months.

Clinical and imaging characteristics

Demographic characteristics (age, sex, vascular risk factors and comorbidities), baseline examination data (blood pressure, heart rate, US National Institutes of Health Stroke Scale (NIHSS) score, glycaemia, temperature), symptom onset to IVT treatment time (OTT), clinical outcomes (24-hour NIHSS score, 3-month mRS score) and imaging characteristics (Alberta Stroke Programme Early CT (ASPECT) score, diffusion-weighted imaging (DWI) ischaemic volume, vascular territory of ischaemia, deep white matter hyperintensities by the FAZEKAS score, susceptibility vessel sign (SVS) or hyper-dense middle cerebral artery sign (HMCAS), SVS or HMCAS length, clot burden score (CBS), thrombus location, FLAIR vascular hyperintensities (FVH)/DWI mismatch[9] and ASPECT-FVH score[10]) were extracted from a centralised database.

The NIHSS score improvement from pretreatment to 24-hour examination was defined by the following criteria: (1) a normalised NIHSS score change (%)[11]; (2) a strong neurological improvement (SNI) defined as 24-hour NIHSS score ≤3; (3) a major neurological improvement (MNI) defined as 24-hour NIHSS score ≤1 or an improvement in NIHSS score ≥8 points; (4) a National Institute of Neurological Disorders and Stroke neurological improvement as an improvement in NIHSS score ≥4 points[12]; (5) NIHSS score improvement of ≥25% at 24 hours and (6) NIHSS score improvement of ≥50% at 24 hours.

Statistical analysis

All analyses involved using SAS/STAT V.9.3 (SAS Institute, Cary, North Carolina, USA). Continuous variables are described with mean±SD or median±IQR and categorical characteristics with frequency (%).

Groups of patients presenting 3-month mRS score 0–1 vs 2–6 were compared in terms of clinical, anamnestic and radiological criteria by Student's t-test, Kruskal-Wallis test, χ^2 test or Fisher's exact test, as appropriate. After multiple imputation, predictors of excellent outcome after IVT alone were assessed by stepwise multivariable logistic regression analysis (significance level for entry=0.2, significance level for removing=0.05), estimating ORs and 95% CIs. To account for differences between CT and MRI, the imaging methods were considered a nesting covariate for each studied imaging characteristic. Multivariate model performance was assessed by the C-statistic.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and their 95% CIs for each definition of 24-hour neurological improvement were computed according to 3-month outcome. Associations between 24-hour NIHSS improvement and 3-month outcome were revealed by multivariable logistic regression analysis using crude ORs and after adjustment for the previous predictors of 3-month outcome as well as age, baseline NIHSS score, 24-hour ASPECT score and Safe Implementation of Thrombolysis in Stroke-Monitoring Study haemorrhage classification.[13] A Bonferroni correction for the inflation of the first-species risk was performed for this second analysis.

RESULTS

Of the 412 patients included in the THRACE trial, 259 received IVT alone: 208 patients were randomised in the IVT group and 200 actually received IVT alone; 204 patients were randomised in the IVT/MT group and 59 did not receive MT and therefore had IVT alone. Of these

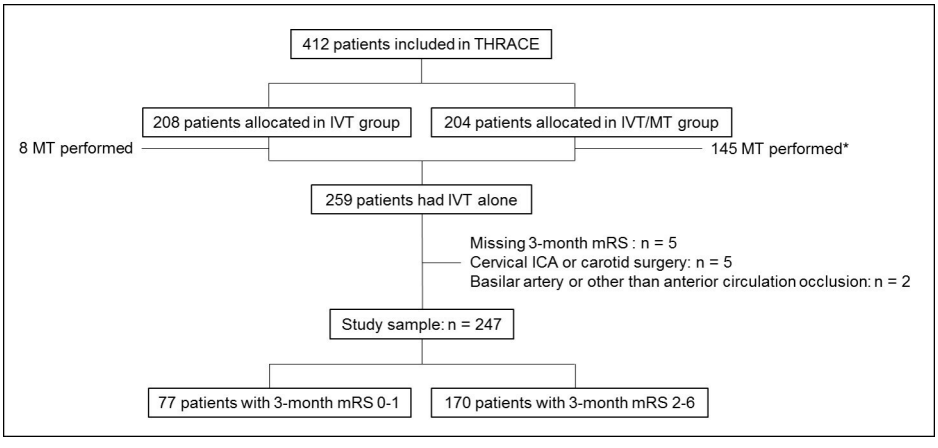

Figure 1 Flow chart. Excellent outcome was defined as a 3-month modified Rankin Scale (mRS) score ≤1. *One of the requirements for mechanical thrombectomy was the absence of neurological improvement ≥4 points between baseline National Institutes of Health Stroke Scale (NIHSS) and NIHSS within 1 hour of IVT. ICA, internal carotid artery occlusion; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; THRACE, Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke.

Table 1 Cohort description and bivariate analysis

	All (n=247)	3-month mRS score 0–1 (n=77)	3-month mRS score 2–6 (n=170)	P value
Sociodemographic features				
Age, n	247/247	77/77	170/170	0.36*
Mean (SD), years	63.8 (13.9)	62.5 (14.2)	64.3 (13.8)	
Median (IQR), years	68.0 (20.0)	66.0 (22.0)	68.5 (18.0)	
Sex, n				
Female, n (%)	121/247	44/77	77/170	0.084†
Comorbidities and risk factors, n				
Diabetes	37/242	8/76	29/166	0.16†
Hypertension	137/244	35/77	102/167	0.022†
Hypercholesterolaemia	125/220	40/72	85/148	0.79†
Renal insufficiency	11/242	1/75	10/167	0.18‡
History of stroke	17/241	5/77	12/164	1.00‡
Coronaropathy	41/233	11/76	30/160	0.38†
Peripheral arterial disease	9/226	2/75	7/151	0.72‡
Current smoking	53/221	12/75	41/146	0.046†
Baseline clinical status				
NIHSS score, n	245/247	77/77	168/170	
Mean (SD), pts	16.9 (4.3)	15.6 (4.1)	17.5 (4.2)	0.0013*
Median (IQR), pts	17.0 (7.0)	15.0 (7.0)	18.0 (7.0)	
Blood pressure, n	244/247	77/77	167/170	
SBP, mean (SD), mm Hg	144 (23)	144 (22)	144 (23)	0.87*
DBP, mean (SD), mm Hg	79 (16)	77 (13)	80 (17)	0.26*
Heart rate, n	242/247	76/77	166/170	
Mean (SD), bpm	75 (17)	75 (16)	76 (17)	0.81*
Glycaemia, n	239/247	75/77	164/170	
Mean (SD), g/L	1.24 (0.38)	1.16 (0.26)	1.27 (0.42)	0.0099*
Temperature, n	237/247	73/77	164/170	
Mean (SD), °C	36.6 (0.5)	36.7 (0.6)	36.6 (0.5)	0.48*
Weight, n	243/247	77/77	166/174	
Mean (SD), kg	75.7 (15.7)	76.3 (14.4)	75.4 (16.3)	0.68*
Baseline imaging characteristics				
Imaging techniques, n				
CT	58/247	14/77	44/170	0.19§
MRI	189/247	63/77	126/170	
Ischaemic core				
ASPECTS score, n	243/247	76/77	167/170	
Mean (SD), pts	7.1 (2.3)	7.8 (1.8)	6.8 (2.5)	0.010§
DWI volume, n	184/189	62/63	122/126	
Mean (SD), mL	40.2 (52.7)	17.0 (16.7)	52.0 (60.3)	0.0003§
Median (IQR), mL	14.8 (44.7)	10.5 (14.0)	19.1 (71.8)	
Vascular territory of ischaemia, n				
Superficial and deep MCA territory	126/237	28/75	98/162	0.0031‡
Superficial MCA	26/237	12/75	14/162	
Deep MCA	78/237	33/75	45/162	
ACA	4/237	0/75	4/162	
Anterior choroid artery	3/237	2/75	1/162	
Microvascular leukopathy				
Fazekas score of DWM, n				

Continued

Table 1 Continued

	All (n=247)	3-month mRS score 0–1 (n=77)	3-month mRS score 2–6 (n=170)	P value
Absence	73/183	30/61	43/122	0.24‡
Punctuate foci	65/183	20/61	45/122	
Beginning confluence	29/183	6/61	23/122	
Large confluent areas	16/183	5/61	11/122	
Thrombus				
Occlusion site, n				
C1	39/240	4/76	35/164	0.0017†¶
M1	199/240	71/76	128/164	
M2	2/240	1/76	1/164	
HMCAS/SVS, n				
Presence versus absence, n	176/234	55/75	121/159	0.65†
Length, mean (SD), mm	14.3 (10.7)	11.3 (8.3)	15.7 (11.4)	0.0008§
Clot burden score, mean (SD), pts	7.0 (1.8)	7.5 (1.5)	6.8 (1.9)	0.0016§
Mismatch				
ASPECT-FVH score, n	151/189	51/63	100/126	0.74§
Mean (SD), pts	3.6 (1.1)	3.5 (1.0)	3.6 (1.1)	
Median (IQR), pts	4.0 (1.0)	4.0 (1.0)	4.0 (1.0)	
FVH/DWI mismatch				
Presence versus absence, n	135/177	53/61	82/116	0.016†
Care workflow time				
Onset-to-Imaging time, n	242/247	76/77	166/170	
Mean (SD), min	116 (43)	110.6 (50.8)	119.0 (39.0)	0.20*
Onset-to-thrombolysis time, n	245/247	77/77	168/170	
Mean (SD), min	153 (40)	142.2 (37.4)	158.0 (41.0)	0.0042*
MRI-to-thrombolysis time, n	241/247	76/77	165/170	
Mean (SD), min	40 (20)	39.4 (20.6)	40.1 (19.4)	0.81*
24-hour clinical and radiological features				
NIHSS score, n	230/247	76/77	154/170	
Mean (SD), pts	11.6 (8.2)	3.7 (3.5)	15.5 (7.0)	<0.0001§
Median (IQR)	11.0 (14.0)	3.0 (6.0)	16.0 (9.0)	
ASPECTS, n	235/247	74/77	161/170	
Mean (SD), pts	5.9 (2.7)	7.6 (1.6)	5.1 (2.8)	<0.0001§
Haemorrhagic classification (SITS-MOST), n				
Absence	163/236	58/74	105/162	0.27‡
Haemorrhagic infarction 1	26/236	7/74	19/162	
Haemorrhagic infarction 2	26/236	5/74	21/162	
Parenchymal haemorrhage 1	11/236	3/74	8/162	
Parenchymal haemorrhage 2	10/236	1/74	9/162	

3-month excellent outcome after IVT alone was defined as a mRS score ≤1.
*Statistical analysis was performed with the Student's t-test.
†χ^2 test.
‡Fisher's exact test.
§Kruskal-Wallis test.
¶Comparison between C1 segment and M1/M2 segment.
ACA, anterior cerebral artery; ASPECT-FVH score (0–6), extent of FLAIR vascular hyperintensities based on ASPECTS territories and without counting insula (higher is better); ASPECTS (0–10), Alberta Stroke Programme Early CT score (higher is better); C1, distal intracranial portion of internal carotid artery; DBP, diastolic blood pressure; DWI volume, diffusion-weighted imaging infarct volume; DWM, deep white matter; FVH/DWI mismatch, FLAIR vascular hyperintensities and diffusion-weighted imaging infarct hyperintensity mismatch; HMCAS, hyper-dense middle cerebral artery sign on CT; M1, first segment of the middle cerebral artery; M2, branches downstream of M1 segment of the middle cerebral artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS score (0–42), National Institutes of Health Stroke Scale score; pts, patients; SBP, systolic blood pressure; SITS-MOST, Safe Implementation of Thrombolysis in Stroke MOnitoring STudY; SVS, susceptibility vessel sign on MRI; clot burden score (0–10): higher is better.

259 patients, 247 were included in our subgroup analysis after excluding 12 patients because of THRACE exclusion criteria (n=5 patients with cervical internal carotid artery occlusion or history of carotid surgery), absence of intracranial anterior circulation occlusion (n=2 basilar artery occlusion or other) and lost to follow-up (n=5 missing 3-month mRS score) (figure 1). Moreover, the 24-hour NIHSS score was available for 230/247 patients.

The mean (SD) age was 63.8 (13.9) years and the male/female sex ratio 1.04. A total of 77/247 (31.2%) patients had an excellent 3-month outcome.

Before multiple imputations, cohort description and bivariate analysis were disclosed in table 1.

After multiple imputations, the bivariate analysis showed the probability of 3-month excellent outcome after IVT alone was associated with no history of hypertension (p=0.02), lower mean glycaemia level (p=0.03), lower mean NIHSS score (p=0.002) and shorter mean OTT (p=0.005) (table 2). On imaging, it was associated with smaller infarction volume on DWI (p<0.002), less often a superficial and deep middle cerebral artery infarct (p=0.02), shorter thrombus length (p=0.02 on MRI, p=0.03 on CT), more frequently M1 occlusion (p=0.005), higher CBS (p=0.005 on MRI, p=0.046 on CT) and more commonly FVH/DWI mismatch (p=0.02) (table 2).

Multivariate analysis allowed for identifying the following factors independently associated with 3-month excellent outcome after IVT alone: no history of hypertension (OR 2.43; 95% CI 1.74 to 3.38; p=0.007), no current smoking (OR 2.76; 95% CI 1.79 to 4.26; p=0.02), shorter OTT (OR 0.47 per hour increase; 95% CI 0.23 to 0.78; p=0.003), smaller DWI volume (OR 0.78 per 10 mL increase; 95% CI 0.68 to 0.89; p=0.0004), presence of SVS (OR 7.89; 95% CI 1.65 to 37.78; p=0.01) and reduced SVS length (OR 0.87 per mm increase; 95% CI 0.80 to 0.94; p=0.001) (table 2). The model allowed for good discrimination, with a C-statistic of 0.79 (95% CI 0.79 to 0.80) and was well calibrated, with Brier score 0.16 and adjusted R^2 0.31.

The normalised NIHSS score change at 24 hours was independently associated with 3-month mRS score 0–1 (adjusted OR 1.79 per 10% increase; 95% CI 1.65 to 1.93; p<0.0001; area under the receiver operating characteristic curve 0.93; 95% CI 0.89 to 0.96) (table 3). With a normalised NIHSS score change threshold set at 35.7% and a Youden Index at 0.71, sensitivity was 0.92, specificity 0.79, PPV 0.69 and NPV 0.95. To anticipate a 3-month excellent outcome, the best specificity and PPV were found with SNI (specificity=0.96; PPV=0.88), MNI (specificity=0.86; PPV=0.73) or NIHSS score improvement ≥50% (specificity=0.85; PPV=0.74) (table 3).

DISCUSSION

Our study provides important information about factors associated with success with IVT alone in patients with stroke with LVO of the anterior circulation. High predictors of 3-month mRS score 0–1 after IVT alone were no medical history of hypertension, no current smoking, reduced OTT, small DWI volume, presence of SVS and short SVS length. In the context of this treatment, this excellent clinical outcome at 3 months can be strongly anticipated by the early NIHSS improvement criteria SNI, MNI and NIHSS improvement of at least 50%.

Factors found associated with 3-month excellent outcome seemed related to time to IVT, thrombus features, effectiveness of leptomeningeal collateral arteries and the resulting seriousness of the infarction before treatment. Current smoking is known to enhance thrombotic effects with increased platelet adherence, endothelial cell damage and the consequent remodelling of parietal vessels. In patients with LVO, these mechanisms prevent the development of leptomeningeal collateral arteries supplying parenchyma.[14 15] Similarly, hypertension would also compromise collateral circulation.[16]

The DWI volume, presence of SVS and SVS length on MRI were the only independent imaging factors associated with the IVT response. Pretreatment infarction volume is an indicator of the seriousness of the stroke and is associated with early and long-term outcome.[17] A lack of leptomeningeal collateral circulation facilitates rapid growth of the ischaemic core. However, the FVH/DWI mismatch seems not an appropriate surrogate of leptomeningeal collateral arteries, nor the ASPECT-FVH score, in predicting 3-month excellent outcome.

Although patients with a large ischaemic core should not be systematically excluded from reperfusion therapy, they are particularly at risk of unfavourable response after IVT alone. This finding is explained in part by the seriousness of cerebral infarction before treatment restricting neurological recovery in the long term, and by absence or delayed reperfusion at the acute phase.[18 19]

From the occlusion characteristics included in the CBS, SVS length emerged as the most determinant factor. This finding may explain the poor response to IVT with intracranial internal carotid artery occlusion.[20] Previous studies have observed a threshold of 8 mm for thrombus length as highly predictive of IVT failure.[20] Presence of SVS was associated with red blood cell-dominant thrombus and IVT effectiveness.[21] OTT is also probably a predictor combining greater chance of reperfusion and lower infarction volume with early IVT instauration.[22]

Another issue of this study was to predict optimal response to IVT with excellent outcome at the long term with early clinical examination after treatment. Previous studies have assessed the success of reperfusion mainly by vascular imaging.[1] Early clinical improvement of patients with stroke with LVO is strongly associated with satisfactory and sustainable reperfusion.[23–26] Consistently, we found a strong association between early and significant clinical improvement after IVT alone and excellent outcome at the long term. Among the different criteria of NIHSS improvement at 24 hours studied, SNI, MNI and NIHSS improvement of at least 50% to anticipate the excellent outcome showed good specificity and PPV. Nevertheless, clinical examination to assess NIHSS score in patients with LVO after IVT has to be performed as fast as possible, and must not delay MT.

The strength of our study lies in the large sample of patients prospectively included in the randomised THRACE study, allowing for a robust analysis of predictors of 3-month excellent outcome after IVT alone. The choice of a dichotomous mRS 1 is supported by the need to increasingly refine the prediction of 3-month favourable outcome for patients

Table 2 Predictors of 3-month excellent outcome after IVT

	3-month mRS score 0–1 (n=77/247)					
	Bivariate (n=247)			Multivariate (n=247)		
	OR	95% CI	P value	OR	95% CI	P value
Sociodemographics features						
Age	0.99	0.97 to 1.01	0.36			
Sex: male versus female	0.62	0.36 to 1.07	0.09			
Comorbidities and risk factors						
Hypertension: absence versus presence	1.87	1.42 to 2.47	**0.024**	2.43	1.74 to 3.38	0.0074
Diabetes: absence versus presence	1.83	0.80 to 4.22	0.15			
Current smoking: absence versus presence	1.86	1.30 to 2.66	0.083	2.76	1.79 to 4.26	0.019
Baseline clinical examination						
NIHSS score, pts*	0.90	0.84 to 0.96	**0.0018**			
Systolic blood pressure, mm Hg*	1.00	0.99 to 1.01	0.91			
Glycaemia, g/L*	0.39	0.17 to 0.92	**0.031**			
Temperature, °C*	1.23	0.74 to 2.05	0.43			
OTT						
Hour*	0.53	0.35 to 0.83	**0.0048**	0.47	0.23 to 0.78	0.0033
Imaging features						
Imaging technique: CT versus MRI	0.64	0.32 to 1.25	0.19			
DWI volume, 10 mL†‡	0.85	0.77 to 0.94	**0.0016**	0.78	0.68 to 0.89	0.0004
Infarct territory			**0.0033**			
Superficial MCA	Reference					
Deep MCA	0.86	0.35 to 2.08	0.73			
Superficial and deep MCA	0.34	0.14 to 0.81	**0.015**			
Other	0.41	0.07 to 2.23	0.30			
Thrombus length‡						
HMCAS length, mm*	0.95	0.91 to 1.00	**0.030**	0.98	0.92 to 1.03	0.37
SVS length, mm*	0.96	0.93 to 0.99	**0.017**	0.87	0.80 to 0.94	0.0012
Occlusion site: M1 versus C1	4.66	1.61 to 13.52	**0.0046**			
Clot burden score‡						
CT, pts*	1.23	1.00 to 1.50	**0.046**			
MRI, pts*	1.26	1.07 to 1.47	**0.0053**			
HMCAS/SVS						
HMCAS: presence versus absence	0.87	0.25 to 2.99	0.83	0.80	0.22 to 2.99	0.74
SVS: presence versus absence	0.84	0.40 to 1.77	0.65	7.89	1.65 to 37.78	0.0097
FVH/DWI mismatch: yes versus no‡	2.71	1.19 to 6.20	**0.018**			
ASPECT-FVH score, pts*‡	1.09	0.93 to 1.27	0.31			
DWM Fazekas score, pts‡						
CT, pts*	0.68	<0.01 to >100	0.99			
MRI, pts*	0.79	0.56 to 1.10	0.16			

3-month excellent outcome after IVT defined by a 3-month mRS score ≤1.
All ORs are calculated for 3-month mRS score ≤2.
Bold values shows p<0.05.
*ORs express the risk variation for a unit increase of the variable.
†ORs express the risk variation for 10 mL increase in the ischaemic core volume on DWI.
‡Nested effect is adjusted on the nesting characteristics, that is, imaging type, to consider effect differently in CT and in MRI.
ASPECTS-FVH score, Alberta Stroke Programme Early CT score and extent of FLAIR vascular hyperintensities (0–6); C1, distal internal carotid artery; clot burden score (0–10); DWI, diffusion-weighted imaging; DWI volume, ischaemic core volume on DWI; DWM Fazekas score, deep white matter Fazekas score (0–3); FVH/DWI mismatch, FLAIR vascular hyperintensity and DWI infarct hyperintensity mismatch; HMCAS/SVS, hyper-dense MCA sign on CT or susceptibility vessel sign on T2*-MRI; IVT, intravenous thrombolysis; M1, first segment of MCA; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke scale; OTT, onset-to-treatment time; pts, patients.

Table 3 Association of 24-hour neurological improvement with 3-month outcome

	3-month mRS score 0–1 (n=76/230)											
	AUC	95% CI	Se	Sp	PPV	NPV	OR*	95% CI	P value	OR†	95% CI	P value
SNI: yes versus no	0.76	0.71 to 0.82	0.57	0.96	0.88	0.82	32.14	12.63 to 81.76	<0.0001	14.35	5.04 to 40.87	<0.0001
MNI: yes versus no	0.82	0.76 to 0.87	0.78	0.86	0.73	0.89	20.82	10.31 to 42.07	<0.0001	26.57	9.52 to 74.19	<0.0001
NINDS NI: yes versus no	0.80	0.76 to 0.85	0.95	0.66	0.58	0.96	35.31	12.22 to 101.99	<0.0001	29.82	8.85 to 100.51	<0.0001
≥25% NI: yes versus no	0.81	0.77 to 0.86	0.96	0.67	0.59	0.97	49.14	14.77 to 163.54	<0.0001	35.50	9.59 to 131.38	<0.0001
≥50% NI: yes versus no	0.85	0.80 to 0.90	0.84	0.85	0.74	0.91	30.38	14.22 to 64.91	<0.0001	20.57	8.45 to 50.05	<0.0001
Normalised change, %‡	0.93	0.89 to 0.96					1.87	1.73 to 2.02	<0.0001	1.79	1.65 to 1.93	<0.0001

Normalised change, calculated as $\frac{(\text{Baseline NIHSS}-24-\text{hour NIHSS})*100}{\text{baseline NIHSS}}$ and as $\frac{(\text{Baseline NIHSS}-24-\text{hour NIHSS})*100}{42-\text{baseline NIHSS}}$, if baseline NIHSS–24-hour NIHSS <0.
Statistical significance requires p<0.004 after Bonferroni correction.
*All ORs and AUC were estimated without adjustment to baseline explaining variables.
†All ORs and AUC were estimated with adjustment on baseline NIHSS, age, 24-hour ASPECT score and SITS-MOST haemorrhage classification, and on factors identified in the previously prediction model.
‡OR express the risk variation for a 10% increase of the variable.
AUC, area under the receiver operating characteristic curve; MNI, major neurological improvement defined as 24-hour NIHSS score ≤1 or a 8-point improvement between baseline and 24-hour NIHSS; mRS, modified Rankin Scale (0–6); 3-month excellent outcome defined as mRS 0–1; ≥25% NI, 24-hour neurological improvement by at least 25% from baseline NIHSS; ≥50% NI, 24-hour neurological improvement by at least 50% from baseline NIHSS; NIHSS, National Institutes of Health Stroke scale; NINDS NI, National Institute of Neurological Disorders and Stroke neurological improvement defined as a 4-point improvement between baseline and 24-hour NIHSS; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; SNI, strong neurological improvement defined as 24-hour NIHSS score ≤3; Sp, specificity.

who benefit from better adapted and more efficient revascularisation strategies. However, some limitations deserve to be mentioned. First, some important data—such as inflammatory and clotting parameters, or previous use of antiplatelet therapy—were not collected. The earliest NIHSS score assessment after treatment was at 24 hours in our study, but studies report that reperfusion, and consequent NIHSS improvement, occurs almost exclusively during the first 2 hours after IVT instauration. However, this estimation can be considered reliable because the patient clinical state was found quite similar between 1 and 24 hours after treatment.[27] We merged data from patients mostly examined with MRI and less with CT but took into account qualitative differences between these imaging techniques in the multivariate analysis.

Predicting the benefit of IVT for patients with LVO to achieve optimal reperfusion remains of high interest. This issue seems different following admission centre. For patients with LVO admitted in a centre without MT capability, IVT represents the first-line treatment in reperfusion strategy. Clinical and radiological criteria associated with optimal response to IVT allow identifying a patient subgroup with high probability to achieve reperfusion during transfer, before planned MT. They can be considered as arguments to help practitioners in decision-making to implement IVT in patients with initial contraindications, nowadays highly debated as elderly, medical history of cerebral haemorrhage, and demonstrated penumbra beyond the time window of 4.5 hours.[4] For patients with LVO admitted in MT capable centres, bridging therapy (including IVT and MT) remains the gold standard. But, relevance of IVT is questioned following recent results from DIRECT-MT (Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals) and DEVT (Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke) trials suggesting MT alone was not non-inferior to bridging therapy.[28 29] However for patients who received IVT in DIRECT-MT, higher frequency of cerebral reperfusion was observed, despite high median OTT. More, non-inferiority was not confirmed by the SKIP trial.[30] Finally, knowledge about factors predicting cerebral reperfusion achievement or failure after IVT could guide research towards new therapeutic strategies. Clinical improvement with reduction of haemorrhagic risk have been reported with alteplase doses lower than the 0.9 mg/kg standard dose, suggesting possible dosage adjustment following patient and stroke characteristics.[31] On the contrary, subgroup of patients with low probability of reperfusion could be candidate to alternative or additional thrombolytics to alteplase. In this way, the EXTEND-IA TNK (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) trial observed a higher rate of reperfusion in patients with LVO after infusion with tenecteplase than alteplase before MT.[32] Safety of glenzocimab, in addition to alteplase at the acute phase of cerebral infarction, is currently assessed.[33]

CONCLUSIONS

Predictors of success with IVT alone in LVO stroke are no medical history of hypertension, no current smoking, reduced OTT, small DWI volume, presence of SVS and short SVS length. These predictors may contribute to identifying patients with high probability to achieve optimal cerebral reperfusion after IVT, and help decision-making in therapeutic strategy. This hypothesis and inherent 3-month excellent outcome can strongly be anticipated by early and significant improvement of the NIHSS score.

Collaborators THRACE investigators: Alain Bonafé, Xavier Leclerc, Nelly Agrinier, Serge Bakchine, Flore Baronnet, Marine Beaumont, Yannick Bejot, Jerome Berge, Marc Bintner, Romain Bourcier, Tae Hee Cho, Frédéric Clarencon, Julien Cogez, Charlotte Cordonnier, Christian Denier, Anne Laure Derelle, Olivier Detante, Xavier Ducrocq, Anthony Faivre, Anne Ferrier, Laetitia Gimenez, Sophie Godard, Benoit Guillon, Emmanuel Houdart, Bertrand Lapergue, Jean-Louis Mas, Thierry Moulin, Mariano Musacchio, Olivier Naggara, Jean Philippe Neau, Michael Obadia, Anne Pasco-Papon, Michel Piotin, Laurent Pierot, Helene Raoult, Frederic Ricolfi, Thomas Ronziere, Guillaume Saliou, Igor Sibon, Sebastien Soize, Jacques Sedat, Christian Stapf, Laurent Suissa, Marie Tisserand, Francis Turjman, Stephane Velasco

Contributors NR-C and SR collected data, performed analysis and drafted the manuscript. BG, SB and FG critically revised the manuscript for substantial changes. MS performed statistical analysis. FZ, YX, LH, GM and CO critically revised the manuscript. All authors have approved the submitted manuscript.

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Data availability statement Data are available on reasonable request. Only data that are relevant for the main objective of this ancillary study were available from the THRACE trial in agreement with the principal investigator of the trial. Individual de-identified participant data were shared following the explanation of the main objective and the statistical analysis. Data are available on reasonable request to SR (s.richard@chru-nancy.fr).

Author note The work has been carried out at Nancy Regional University Hospital, France.

ORCID iDs
Marc Soudant http://orcid.org/0000-0001-5814-6924
Sébastien Richard http://orcid.org/0000-0002-0945-5656

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