



HAL
open science

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

Nolwenn Riou-Comte, Benjamin Gory, Marc Soudant, François Zhu, Yu Xie, Lisa Humbertjean, Gioia Mione, Catherine Oppenheim, Francis Guillemin, Serge Bracard, et al.

► **To cite this version:**

Nolwenn Riou-Comte, Benjamin Gory, Marc Soudant, François Zhu, Yu Xie, et al.. Clinical imaging factors of excellent outcome after thrombolysis in large-vessel stroke: a THRACE subgroup analysis. *Stroke and Vascular Neurology*, 2021, 6 (4), pp.631-639. 10.1136/svn-2020-000852 . hal-04212238

HAL Id: hal-04212238

<https://hal.science/hal-04212238>

Submitted on 20 Sep 2023



HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

To cite: Riou-Comte N, Gory B, Soudant M, *et al.* Clinical imaging factors of excellent outcome after thrombolysis in large-vessel stroke: a THRACE subgroup analysis. *Stroke & Vascular Neurology* 2021;**6**: e000852. doi:10.1136/svn-2020-000852

Received 31 December 2020
Revised 9 April 2021
Accepted 14 April 2021
Published Online First
8 June 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Neurology-Stroke Unit, CIC-P 1433, INSERMU1116, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France

²Department of Diagnostic and Therapeutic Neuroradiology, INSERM U1254, IADI, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France

³Clinical Investigation Centre-Clinical Epidemiology 1433, INSERM, Université de Lorraine, Nancy Regional University Hospital Center, Nancy, France

⁴Department 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 mismatch⁹ and ASPECT-FVH score¹⁰) 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 points¹²; (5) NIHSS score improvement of $\geq 25\%$ at 24 hours and (6) NIHSS score improvement of $\geq 50\%$ 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 \pm SD or median \pm 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

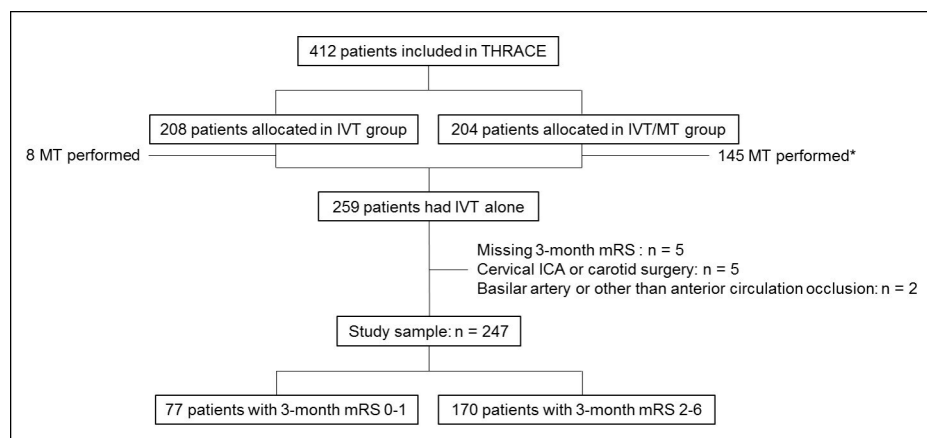


Figure 1 Flow chart. Excellent outcome was defined as a 3-month modified Rankin Scale (mRS) score ≤ 1 . *One of the requirements for mechanical thrombectomy was the absence of neurological improvement ≥ 4 points between baseline National Institutes of Health Stroke Scale (NIHSS) and NIHSS within 1 hour 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				
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				
Mean (SD), bpm	75 (17)	75 (16)	76 (17)	0.81*
Glycaemia, n				
Mean (SD), g/L	1.24 (0.38)	1.16 (0.26)	1.27 (0.42)	0.0099*
Temperature, n				
Mean (SD), °C	36.6 (0.5)	36.7 (0.6)	36.6 (0.5)	0.48*
Weight, n				
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				
<i>Occlusion site, n</i>				
C1	39/240	4/76	35/164	0.0017†¶
M1	199/240	71/76	128/164	
M2	2/240	1/76	1/164	
<i>HMCAS/SVS, n</i>				
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				
<i>ASPECT-FVH score, n</i>				
Mean (SD), pts	151/189	51/63	100/126	0.74§
Median (IQR), 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)	
<i>FVH/DWI mismatch</i>				
Presence versus absence, n	135/177	53/61	82/116	0.016†
Care workflow time				
Onset-to-Imaging time, n				
Mean (SD), min	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				
Mean (SD), min	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				
Mean (SD), min	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				
Mean (SD), pts	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				
Mean (SD), pts	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 $\geq 50\%$ (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 $\frac{(\text{Baseline NIHSS}-24\text{-hour NIHSS})\times 100}{\text{baseline NIHSS}}$ and as $\frac{(\text{Baseline NIHSS}-24\text{-hour NIHSS})\times 100}{42 - \text{baseline NIHSS}}$, 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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study is a subgroup analysis of the THRACE trial having received the required legal approval from the “Comité de Protection des Personnes III”, Nord Est Ethics Committee, and the research boards of the participating centres with 2009-A00753-54. All patients or their legal representatives provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

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.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Marc Soudant <http://orcid.org/0000-0001-5814-6924>

Sébastien Richard <http://orcid.org/0000-0002-0945-5656>

REFERENCES

- 1 Seners P, Turc G, Maier B. Incidence and predictors of early recanalization after intravenous thrombolysis: a systematic review and meta-analysis. *Stroke* 2016;47:2409–12.
- 2 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–8.

- 3 Hacke W, Kaste M, Bluhmki E, *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
- 4 Berge E, Whiteley W, Audebert H, *et al.* European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:1–LXII.
- 5 Turc G, Apoil M, Naggara O, *et al.* Magnetic resonance Imaging-DRAGON score: 3-month outcome prediction after intravenous thrombolysis for anterior circulation stroke. *Stroke* 2013;44:1323–8.
- 6 Baek JH, Kim K, Lee Y-B, *et al.* Predicting stroke outcome using clinical- versus imaging-based scoring system. *J Stroke Cerebrovasc Dis* 2015;24:642–8.
- 7 Hernández-Pérez M, Pérez de la Ossa N, Aleu A, *et al.* Natural history of acute stroke due to occlusion of the middle cerebral artery and intracranial internal carotid artery. *J Neuroimaging* 2014;24:354–8.
- 8 Bracard S, Ducrocq X, Mas JL, *et al.* Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138–47.
- 9 Legrand L, Tisserand M, Turc G, *et al.* Fluid-Attenuated inversion recovery vascular Hyperintensities-Diffusion-Weighted imaging mismatch identifies acute stroke patients most likely to benefit from recanalization. *Stroke* 2016;47:424–7.
- 10 Nave AH, Kufner A, Bücke P, *et al.* Hyperintense vessels, collateralization, and functional outcome in patients with stroke receiving endovascular treatment. *Stroke* 2018;49:675–81.
- 11 Balucani C, Levine SR, Khoury JC, *et al.* Acute ischemic stroke with very early clinical improvement: a national Institute of neurological disorders and stroke recombinant tissue plasminogen activator stroke trials exploratory analysis. *J Stroke Cerebrovasc Dis* 2016;25:894–901.
- 12 Grotta JC, Welch KM, Fagan SC, *et al.* Clinical deterioration following improvement in the NINDS rt-PA stroke trial. *Stroke* 2001;32:661–8.
- 13 Wahlgren N, Ahmed N, Dávalos A, *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in Stroke-Monitoring study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82.
- 14 Shuaib A, Butcher K, Mohammad AA, *et al.* Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol* 2011;10:909–21.
- 15 Béjot Y, Jacquin A, Daubail B, *et al.* Smoking status and severity of ischemic stroke. A population-based study. *Eur Neurol* 2014;71:59–64.
- 16 Chan S-L, Sweet JG, Bishop N, *et al.* Pial collateral reactivity during hypertension and aging: understanding the function of collaterals for stroke therapy. *Stroke* 2016;47:1618–25.
- 17 Barrett KM, Ding YH, Wagner DP, *et al.* Change in diffusion-weighted imaging infarct volume predicts neurologic outcome at 90 days: results of the acute stroke accurate prediction (ASAP) trial serial imaging substudy. *Stroke* 2009;40:2422–7.
- 18 Gautheron V, Xie Y, Tisserand M, *et al.* Outcome after reperfusion therapies in patients with large baseline diffusion-weighted imaging stroke lesions: a THRACE trial (mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke) subgroup analysis. *Stroke* 2018;49:750–3.
- 19 Humpich M, Singer OC, du Mesnil de Rochemont R, *et al.* Effect of early and delayed recanalization on infarct pattern in proximal middle cerebral artery occlusion. *Cerebrovasc Dis* 2006;22:51–6.
- 20 Riedel CH, Zimmermann P, Jensen-Kondering U, *et al.* The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* 2011;42:1775–7.
- 21 Choi MH, Park GH, Lee JS, *et al.* Erythrocyte fraction within retrieved thrombi contributes to thrombolytic response in acute ischemic stroke. *Stroke* 2018;49:652–9.
- 22 Fonarow GC, Zhao X, Smith EE, *et al.* Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA* 2014;311:1632–40.
- 23 Rha J-H, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke* 2007;38:967–73.
- 24 Khatri P, Neff J, Broderick JP, *et al.* Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. *Stroke* 2005;36:2400–3.
- 25 Zaidat OO, Yoo AJ, Khatri P, *et al.* Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650–63.
- 26 Eilaghi A, Brooks J, d'Este C, *et al.* Reperfusion is a stronger predictor of good clinical outcome than recanalization in ischemic stroke. *Radiology* 2013;269:240–8.
- 27 Takagi T, Kato T, Sakai H, *et al.* Early neurologic improvement based on the National Institutes of health stroke scale score predicts favorable outcome within 30 minutes after undergoing intravenous recombinant tissue plasminogen activator therapy. *J Stroke Cerebrovasc Dis* 2014;23:69–74.
- 28 Yang P, Zhang Y, Zhang L, *et al.* Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
- 29 Zi W, Qiu Z, Li F, *et al.* Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234–43.
- 30 Suzuki K, Matsumaru Y, Takeuchi M, *et al.* Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244–53.
- 31 Dong Y, Han Y, Shen H, *et al.* Who may benefit from lower dosages of intravenous tissue plasminogen activator? Results from a cluster data analysis. *Stroke Vasc Neurol* 2020;5:348–52.
- 32 Campbell BCV, Mitchell PJ, Churilov L, *et al.* Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573–82.
- 33 Renaud L, Lebozec K, Voors-Pette C, *et al.* Population pharmacokinetic/pharmacodynamic modeling of Glenzocimab (ACT017) a glycoprotein VI inhibitor of collagen-induced platelet aggregation. *J Clin Pharmacol* 2020;60:1198–208.