

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

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Background and Purpose—Stroke patients with large diffusion-weighted imaging (DWI) volumes are often excluded from reperfusion because of reckoned futility. In those with DWI_{volume} >70 mL, included in the THRACE trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke), we report the associations between baseline parameters and outcome.

Methods—We examined 304 patients with anterior circulation stroke and pretreatment magnetic resonance imaging. Variables were extracted from the THRACE database, and DWI volumes were measured semiautomatically.

Results—Among 53 patients with DWI_{volume} >70 mL, 12 had favorable outcome (modified Rankin Scale score, ≤2) at 3 months; they had less coronary disease (0/12 versus 12/38; *P*=0.046) and less history of smoking (1/10 versus 12/31; *P*=0.013) than patients with modified Rankin Scale score >2. None of the 8 patients >75 years of age reached modified Rankin Scale score ≤2. Favorable outcome occurred in 12 of 37 M1-occluded patients but in 0 of 16 internal carotid-T/L-occluded patients (*P*=0.010). Favorable outcome was more frequent (6/13) when DWI lesion was limited to the superficial middle cerebral artery territory than when it extended to the deep middle cerebral artery territory (6/40; *P*=0.050).

Conclusions—Stroke patients with DWI lesion >70 mL may benefit from reperfusion therapy, especially those with isolated M1 occlusion or ischemia restricted to the superficial middle cerebral artery territory. The benefit of treatment seems questionable for patients with carotid occlusion or lesion extending to the deep middle cerebral artery territory. (*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020244.)

Key Words: ischemia ■ magnetic resonance imaging ■ outcome ■ recanalization ■ stroke

The prognosis of acute ischemic stroke because of large vessel occlusion with large baseline lesion's volume is known to be ominous. Because clinical benefit is uncertain,^{1,2} these patients were excluded or underrepresented in recent thrombectomy trials.³ In the THRACE trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke),⁴ patients were not selected by lesion size. Consequently, 57 patients had large lesion based on low (<5) Alberta Stroke Program Early CT Score (ASPECTS).⁴ Interestingly, 17 patients had 3-month favorable outcome (modified Rankin Scale [mRS] score, ≤2), suggesting they may actually derive benefit from reperfusion, in line with previous mono- and bicenter studies.⁵⁻⁸ Ischemic lesion volume is more accurately assessed by direct diffusion-weighted imaging

(DWI) measurements than by ASPECTS.⁹ Using magnetic resonance imaging-selected patients of the THRACE trial, we searched for baseline parameters associated with favorable outcome in those with large DWI lesions, focusing on pre-defined 70- and 100-mL cutoffs.^{2,6-8,10}

Patients and Methods

THRACE⁴—a multicenter randomized controlled trial in France— included patients 18 to 80 years of age with acute ischemic stroke because of proximal occlusion, randomly assigned to receive either intravenous thrombolysis or thrombolysis plus thrombectomy. We selected patients with anterior circulation stroke and occlusion of the intracranial internal carotid artery (ICA) or M1 portion of the middle cerebral artery (MCA) on pretreatment magnetic resonance imaging. DWI_{volume} was determined semiautomatically on Olea Sphere (V3.0;

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Olea Medical, La Ciotat, France). After motion correction and cerebrospinal fluid masking, a threshold of apparent diffusion coefficient $<0.6 \times 10^{-3} \text{ mm}^2/\text{s}$ was applied to the ADC map, with manual adjustment of lesion boundaries in consensus by 2 neuroradiologists when appropriate. Other variables were extracted from the THRACE database. DWI lesions of the MCA territory were classified as deep when involving the caudate, lentiform nuclei or internal capsule or superficial, otherwise. Patients with mRS score ≤ 2 and > 2 were compared in the DWI_{volume} >70 - and >100 -mL subgroups in univariate analysis (Student *t* test or Mann–Whitney *U* test for quantitative variables and χ^2 test or Fisher exact test for qualitative variables). Inclusion/exclusion criteria and ethics statement of THRACE trial⁴ are provided in Methods in the [online-only Data Supplement](#). The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Among 414 randomized patients in the THRACE trial, 110 were excluded (108 without pretreatment magnetic resonance imaging, 2 vertebrobasilar strokes). Of the 304 included patients, 56 (18.4%) presented DWI_{volume} >70 mL and 37 (12.5%) >100 mL. A comparison between patients with DWI_{volume} ≤ 70 mL and those with DWI_{volume} >70 mL is provided in Table I in the [online-only Data Supplement](#).

In patients with DWI_{volume} >70 mL, 12 of 53 had 3-month mRS score ≤ 2 (3 patients lost to follow-up; Table). Patients with mRS score ≤ 2 had less coronary disease (0/12 versus 12/38; $P=0.046$) and less history of smoking (1/10 versus 12/31; $P=0.013$). All 8 patients >75 years of age had 3-month mRS score >2 . Favorable outcome occurred in 12 of 37 patients with M1 occlusions but in none of the 16 ICA-T/L occlusions ($P=0.010$). This difference in outcome was not explained by concomitant anterior cerebral arterial territory lesions that were equally observed in M1- (5/37) and ICA- (2/16) occluded patients. Favorable outcome was more frequent in patients with DWI lesion limited to the superficial MCA territory (6/13) than when it also involved the deep MCA territory (6/40; $P=0.050$; Figure). Six of 10 patients with M1 occlusion and DWI lesion limited to the superficial MCA territory had favorable outcome. In patients with DWI_{volume} >70 mL, lesion lateralization and randomization group did not differ between those with favorable and unfavorable outcomes. In an intention-to-treat analysis (3 patients with missing 3-month mRS score considered as unfavorable outcome), patients with mRS score ≤ 2 had less coronary disease, higher DWI-ASPECTS, and less ICA-T/L occlusion (Table II in the [online-only Data Supplement](#)). In the DWI_{volume} >100 -mL subgroup, 8 of 37 patients had an mRS score ≤ 2 . All significant associations observed in the DWI_{volume} >70 mL-subgroup were maintained except for coronary disease.

Discussion

In the THRACE population, 12 of 53 patients achieved favorable outcome, despite pretreatment DWI_{volume} >70 mL. This result is similar to rates reported by others using DWI_{volume} >70 mL^{6–8} or core >70 mL on computed tomographic perfusion maps,¹¹ despite disparities in the administered treatment. Our results question the 70-mL cutoff reliability because the proportion of patients with favorable outcome was similar in the >100 - and >70 -mL subgroups, in line with others.⁶ Interestingly, above the 70- or 100-mL cutoff, DWI_{volume} was not significantly different

Table. Three-Month Outcome in Patients With DWI_{volume} >70 mL

	mRS Score ≤ 2 , n=12	mRS Score > 2 , n=41	P Value
Age, y	53.5 [44.2–68]	65 [50–72.5]	0.149
Women	3/12 (25)	18/41 (43.9)	0.239
Hypertension	5/12 (41.7)	20/41 (48.8)	0.664
History of smoking	1/10 (10)	12/31 (38.7)	0.013
Hypercholesterolemia	8/12 (66.7)	16/35 (45.7)	0.210
Diabetes mellitus	0/12 (0)	8/41 (19.5)	0.097
Coronary disease	0/12 (0)	11/38 (29)	0.046
Baseline glycemia, g/L	1.2 [1–1.3]	1.3 [1.1–1.5]	0.285
Baseline NIHSS score	18.5 [18–21.7]	20 [18.5–22]	0.691
Left hemisphere	5/12 (41.7)	25/41 (61)	0.235
ICA-T/L occlusion	0/12 (0)	16/41 (39)	0.010
Deep and superficial MCA territory	6/12 (50)	34/41 (82.9)	0.050
DWI-ASPECTS	4.5 [3–5.7]	3 [2–5]	0.033
DWI _{volume} , mL	106.4 [85.5–149.8]	127.7 [91.0–163.4]	0.548
Onset-to-MRI delay, min	106.5 [80.5–120]	116 [95.5–138.5]	0.254
Onset-to-thrombolysis delay, min	146.4 [114–170.4]	153 [133.8–172.8]	0.343
Thrombolysis and thrombectomy	5/12 (41.7)	16/41 (39.0)	0.958
Reperfusion mTICI 2b-3	2/4 (50)	5/13 (38.5)	0.682
Any 24-h hemorrhage	0/12 (0)	13/40 (32.5)	0.024
Symptomatic 24-h hemorrhage	0/12 (0)	3/35 (8.6)	0.560

Data are presented as n (%) or median [IQR]. ASPECTS indicates Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; mTICI, modified treatment in cerebral infarction; and NIHSS, National Institutes of Health Stroke Scale.

between patients with and without favorable outcomes, suggesting that a simple DWI_{volume} cutoff is insufficient to exclude patients for treatment.⁶ As in 2 previous studies,^{6,11} all patients >75 years of age with large baseline volumes had unfavorable outcome, suggesting that age could be an additional factor to guide treatment decision-making. Risk factors for atherosclerosis including history of smoking and coronary disease were more frequent in patients with unfavorable outcome. This may be because of a poorer collateral network, lower fibrin clot permeability, more difficult access to the clot during catheterization, and thus higher risk of infarct growth.

An original although expected finding was the association between unfavorable outcome and deep MCA territory involvement. The capsulostratial regions play a key prognostic role in motor recovery and because of their small size, weigh more in ASPECTS than in DWI_{volume}. This likely explains why, in large DWI lesions, ASPECTS remained associated with outcome, whereas DWI_{volume} did not. ASPECTS is also

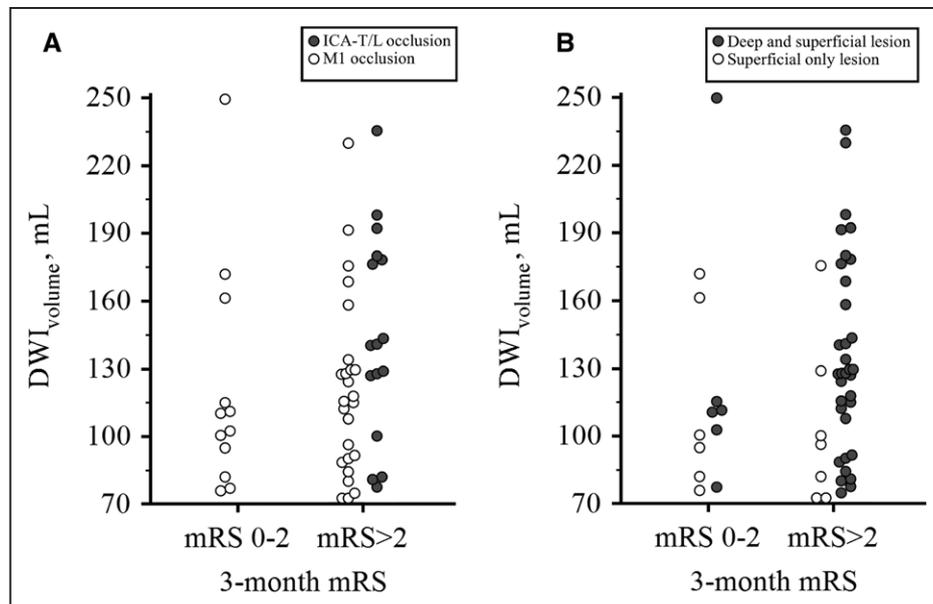


Figure. Baseline diffusion-weighted imaging (DWI) volume and 3-mo outcome (modified Rankin Scale [mRS] score >2, unfavorable) in the 53 patients with $DWI_{\text{volume}} > 70$ mL according to (A) occlusion site, (B) involvement of the deep or superficial middle cerebral artery territory. ICA indicates internal carotid artery.

independent of the total brain volume, while a given lesion volume could have a different clinical meaning in young patients without brain atrophy than in older patients, in whom 70 mL of tissue represents a larger proportion of the entire brain. The frequent involvement of deep MCA territory likely explains the higher frequency of any type of hemorrhagic transformation in patients with unfavorable outcome because deep MCA infarcts are prone to petechial hemorrhage after recanalization.¹²

Finally, ICA-T/L occlusion is a well-known factor of poor outcome after stroke,¹³ but this association has never been studied in patients with $DWI_{\text{volume}} > 70$ mL. Strikingly, none of the 16 patients with ICA occlusion had favorable outcome, which conversely occurred in one third of patients with M1 occlusion. In the only study reporting poor outcome in all 6 $DWI_{\text{volume}} > 70$ mL patients, despite successful reperfusion in 3 of them, all had an ICA occlusion.²

Our study has several limitations: (1) given the THRACE trial design, reperfusion status, which plays a major role in predicting outcome,⁵⁻⁸ was lacking in patients who did not receive thrombectomy; (2) we did not differentiate between ICA-T and ICA-L occlusions or between proximal and distal M1 occlusions; (3) our results do not apply to patients imaged well beyond the IV-thrombolysis time window because magnetic resonance imaging was obtained within 4 hours after onset. Likely, DWI lesions have different tissue fate and prognosis value if captured at an early time point or later on, owing to the DWI reversibility phenomenon that is more frequent and sizeable in the early time frame^{8,14}; and (4) although multicenter and prospective, the THRACE trial was not designed for the purpose of our analysis, which does not allow conclusions to be made about the optimal treatment in large DWI lesions. The small sample size precluded multivariate analysis. Pooled analysis of studies with large DWI will help clarify which of the above parameters are independent prognostic factors. Planned randomized studies for patients with large

infarcts will help elucidate the link between early reperfusion and outcome.

Our multicenter data suggest that patients with M1 occlusion or ischemia restricted to the superficial MCA territory may benefit from reperfusion therapies, despite large DWI lesion. Conversely, the benefit seems questionable for patients with carotid occlusion or DWI lesion extending to the deep MCA territory. Validation in larger cohorts is warranted.

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Disclosures

None.

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Stroke

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SUPPLEMENTAL MATERIAL

Outcome after reperfusion therapies in patients with large baseline DWI stroke lesions. A THRACE trial subgroup analysis

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Cover Title: Outcome in large DWI volume stroke lesion

2 Tables

Key Words: MRI, Acute Stroke, diffusion-weighted imaging, ischemia

Subject Codes: Magnetic Resonance Imaging. Ischemic Stroke. Revascularization

SUPPLEMENTAL METHODS

Complete inclusion and exclusion criteria of mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke THRACE trial¹

Inclusion criteria:

Age 18 to 80 years

No more than four hours since symptom onset

NIHSS score ≥ 10 and ≤ 25

Occlusion of the intra cranial internal carotid artery (ICA), the initial segment of middle cerebral artery (M1 segment) or the superior third of the basilar artery

Exclusion criteria:

General or acute ischemic stroke-specific contraindications to alteplase according to French guidelines

Treatment initiated more than four hours after ischemic stroke symptom onset or when the time of symptom onset is unknown

Any conditions that may be life-threatening within the following three months

Any situations making patient follow-up impossible (patients who are homeless, foreigners, etc.)

History of iliofemoral surgery and by extension any local conditions making femoral catheterization impossible

Occlusion or preocclusive stenosis of the cervical segment of the ICA ipsilateral to the lesion

Hyperdensities or other signal abnormalities suggesting hemorrhage regardless of severity

Intracranial tumours other than small meningiomas

Infarct with a mass effect causing midline shift already visible on CT or MRI FLAIR, indicating an error in amount of time since symptom onset

Contraindications specific to the employed thrombectomy system

Ethics

The study protocol of mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE) trial¹ was approved by the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent.

SUPPLEMENTAL TABLES

Online supplemental Table I. Baseline characteristics and outcomes

	All population n=304	DWI-volume\leq70mL n=248	DWI-volume$>$70mL n=56	P-value
Age, years	67 [54-74]	68 [55-75]	61.5 [45.5-70.8]	0.016
Women	145/304 (47.7)	123/248 (49.7)	22/56 (39.3)	0.163
Hypertension	155/301 (51.5)	128/245 (52.2)	27/56 (48.2)	0.586
Past smoking	51/264 (19.3)	38/220 (17.3)	13/44 (29.6)	0.06
Hypercholesterolemia	142/271 (52.4)	117/221 (53)	25/50 (50.0)	0.707
Diabetes mellitus	31/301 (10.3)	22/245 (9)	9/56 (16.0)	0.115
Coronary disease	42/290 (14.5)	30/237 (12.7)	12/53 (22.6)	0.062
Baseline glycemia, g/L	1.17 [1.0-1.4]	1.16 [1.0-1.4]	1.20 [1.0-1.4]	1.000
Baseline NIHSS score	18 [14-20]	17 [13-20]	19.5 [18-22]	<0.001
Left hemisphere	145/304 (47.8)	115/248 (46.4)	30/56 (53.6)	0.330
ICA-T/-L occlusion	47/304 (15.5)	31/248 (12.5)	16/56 (28.6)	0.003
MCA ischemic territory lesion				
Superficial	208/304 (68.4)	153/248 (61.7)	56/56 (100)	<0.001
Deep and superficial	173/304 (56.9)	131/248 (52.8)	42/56 (75.0)	0.003
DWI-ASPECTS	7 [5-9]	8 [6-9]	3 [2-5]	<0.001
DWI _{volume} , mL	17.2 [9.3-52.5]	13.90 [7.3-29.1]	115.48 [89.2-154.5]	<0.001
Onset-to-MRI delay, min	114 [90-138]	114 [90-138]	114 [96-138]	0.522
Onset-to-thrombolysis delay, min	150 [126-180]	150 [120-180]	156 [126-174]	0.703
Thrombolysis and thrombectomy	149/304 (49.0)	92/248 (37.1)	20/56 (35.7)	0.846
Reperfusion mTICI 2b-3	74/104 (71.2)	22/86 (25.6)	7/18 (38.9)	0.252
mRS score 0-2	142/298 (51.0)	140/245 (57.1)	12/53 (22.6)	<0.001
Death	34/298 (11.4)	15/245 (6.1)	18/53 (34.0)	<0.001
Any 24hr hemorrhage	45/295 (15.2)	32/241 (13.3)	13/54 (24.1)	0.046
Symptomatic 24hr hemorrhage	6/282 (2.1)	3/233 (1.3)	3/49 (6.1)	0.067

Data are presented as n/N(%) or median [IQR]. mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT-Score. P-values were calculated between DWI_{volume \leq 70mL} and DWI_{volume $>$ 70mL} groups.

Online supplemental Table II. 3-month outcome in Patients with DWI_{volume}>70mL. Intention-to-treat analysis*

	mRS≤2, n=12	mRS>2, n=44	P-value
Age, years	53.5 [44.2-68]	65 [49.5-73.8]	0.159
Women	3/12 (25)	19/44 (43.2)	0.329
Hypertension	5/12 (41.7)	22/44 (50)	0.748
History of smoking	1/10 (10)	12/34 (35.3)	0.237
Hypercholesterolemia	8/12 (66.7)	17/38 (44.7)	0.321
Diabetes mellitus	0/12 (0)	9/44 (19.5)	0.180
Coronary disease	0/12 (0)	12/41 (29.3)	0.048
Baseline glycemia, g/L	1.2 [1-1.3]	1.3 [1-1.5]	0.214
Baseline NIHSS score	18.5 [18-21.7]	20 [18-22]	0.740
Left hemisphere	5/12 (41.7)	25/44 (56.8)	0.515
ICA-T/-L occlusion	0/12 (0)	16/44 (36.4)	0.012
Deep and superficial MCA territory	6/12 (50)	36/44 (81.8)	0.054
DWI-ASPECTS	4.5 [3-5.7]	3 [2-5]	0.033
DWI _{volume} , mL	106.4 [85.5-149.8]	125.6 [89.1-154.5]	0.448
Onset-to-MRI delay, min	106.5 [80.5-120]	115 [94.3-138.8]	0.281
Onset-to-thrombolysis delay, min	146.4 [114-170.4]	153 [129.2-173.7]	0.522
Thrombolysis and thrombectomy	5/12 (41.7)	17/44 (38.6)	1
Reperfusion mTICI 2b-3	2/4 (50)	5/14 (35.7)	1
Any 24hr hemorrhage	0/12 (0)	13/42 (31)	0.050
Symptomatic 24hr hemorrhage	0/12 (0)	3/37 (8.1)	0.566

Data are presented as n/N (%) or median [IQR]. mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT-Score. *Three patients with missing 3-month mRS are considered in the unfavorable outcome group.

SUPPLEMENTAL REFERENCES

1. Bracad S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138-1147.