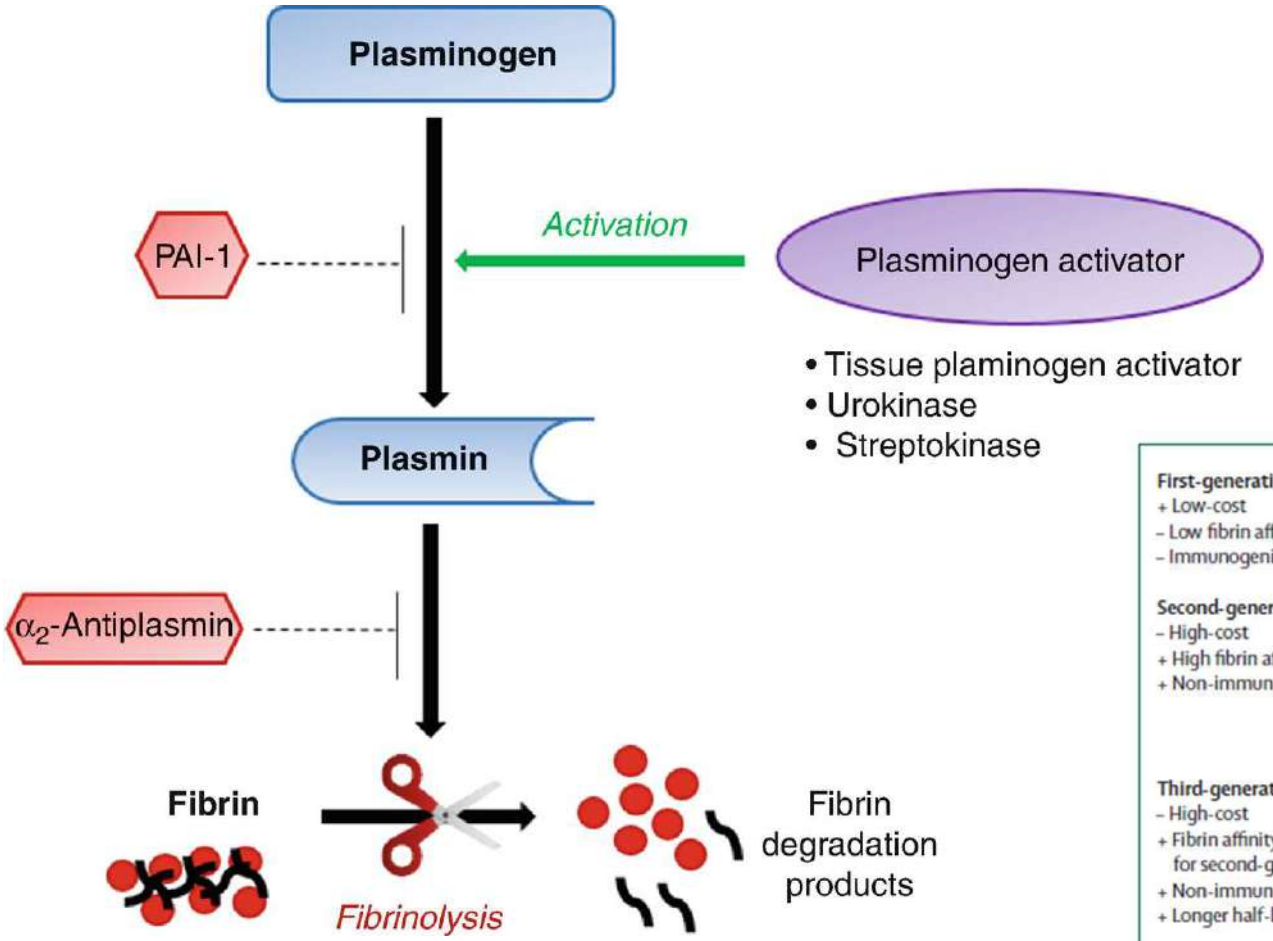
La thrombolyse IV en 2025

- **Encore ?**
- **Quand ?**
- **Quoi ?**
- **Qui ?**

Pr Sébastien RICHARD



	Time	
First-generation agent + Low-cost – Low fibrin affinity – Immunogenic		• **Streptokinase: intravenous administration (1·5 million units)**[10] – Increased morbidity and mortality (compared with placebo)
Second-generation agents – High-cost + High fibrin affinity + Non-immunogenic		• **Alteplase: intravenous administration (0·9 mg/kg)**[11,12] **or intra-arterial administration (0·225 mg/kg)**[13] + Improved clinical outcomes (compared with placebo) • **Prourokinase: intra-arterial administration (9 mg plus heparin)**[14] + Improved reperfusion and clinical outcomes (compared with placebo)
Third-generation agents – High-cost + Fibrin affinity higher than for second-generation agents + Non-immunogenic + Longer half-life		• **Desmoteplase: intravenous administration (90 μg/kg)**[15] + No change in clinical outcomes & no safety concerns (compared to placebo) • **Staphylokinase: intravenous administration (10 mg)**[16] + Non-inferior to alteplase in efficacy and similar safety • **Tenecteplase: intravenous administration (0·25 mg/kg)**[17] + Non-inferior to alteplase in efficacy and comparable safety

Figure 1: **Thrombolytic agents for the treatment of acute ischaemic stroke**
Repeat exposure to immunogenic agents can cause severe allergic reactions, including anaphylaxis. Schematic overview of the results of major trials of thrombolytic agents, from early first-generation agents to current third-generation drugs. High fibrin affinity translates into greater potency for thrombolysis, at the same time preserving the integrity of systemic coagulation. +=advantage of the agent. –=disadvantage of the agent.

Les dogmes de la TIV

Table 1. Major Inclusion and Exclusion Criteria.

Main inclusion criteria
Acute ischemic stroke
Age, 18 to 80 years
Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration
Stroke symptoms present for at least 30 minutes with no significant improvement before treatment
Main exclusion criteria
Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000 per cubic millimeter
Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral-artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

HCS 2.4 à 6.4%

The NEW ENGLAND JOURNAL of MEDICINE

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Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.68). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

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*The European Cooperative Acute Stroke Study (ECASS) investigators are listed in the Appendix.

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N Engl J Med 2008;359:1317-29.

Les avancées rapides de la TM

Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial

Serge Bracard, Xavier Ducrocq, Jean Louis Mas, Marc Soudant, Catherine Oppenheim, Thierry Moulin, Francis Guillemin, on behalf of the THRACE investigators*

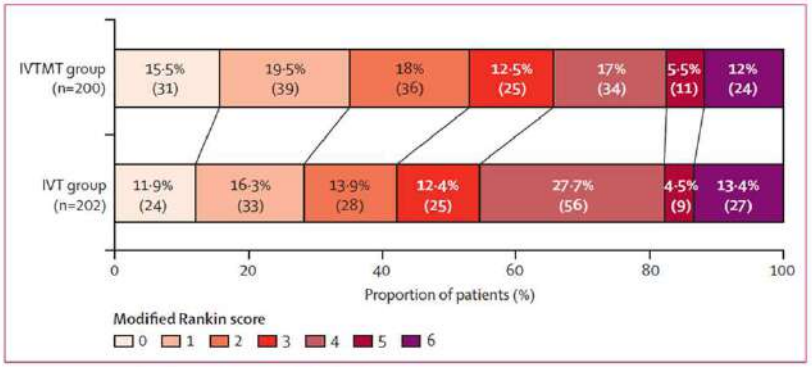

Figure 2: **Functional independence (modified Rankin score) at 3 months**
Data are proportion of patients (n). IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy.

Rankin ≤2: IV 42% *vs.* IVIA 53%

HCS 2%

2015 : Avènement de la thrombectomie

Study or subgroup	No of events/total: Endovascular treatment (including AIMT)	No of events/total: Medical care	Risk ratio (95% CI) M-H, random	Weight (%)	Risk ratio (95% CI) M-H, random
2013					
IMS III	177/434	86/222		13.4	1.05 (0.86 to 1.29)
MR RESCUE	12/64	11/54		4.4	0.92 (0.44 to 1.92)
SYNTHESIS	76/181	84/181		12.7	0.90 (0.72 to 1.14)
Subtotal (95% CI)	265/679	181/457		30.4	0.98 (0.85 to 1.14)
Test for heterogeneity: τ^2=0.00, χ^2=0.97, df=2, P=0.62, I^2=0%					
Test for overall effect: z=0.21, P=0.83					
2015					
ESCAPE	89/164	43/147		11.4	1.86 (1.39 to 2.47)
EXTEND-IA	25/35	14/35		7.9	1.79 (1.13 to 2.82)
MR CLEAN	77/233	51/267		10.9	1.73 (1.27 to 2.35)
SWIFT PRIME	59/98	33/93		10.7	1.70 (1.23 to 2.33)
REVASCAT	45/103	29/103		9.4	1.55 (1.06 to 2.27)
THERAPY	19/55	14/53		6.1	1.31 (0.73 to 2.33)
THRACE	103/109	82/195		13.2	1.29 (1.04 to 1.59)
Subtotal (95% CI)	417/878	266/893		69.6	1.56 (1.38 to 1.75)
Test for heterogeneity: τ^2=0.00, χ^2=5.98, df=6, P=0.43, I^2=0%					
Test for overall effect: z=7.24, P<0.001					
Total (95% CI)	682/1557	447/1350		100.0	1.37 (1.14 to 1.64)
Test for heterogeneity: τ^2=0.05, χ^2=29.12, df=9, P<0.001, I^2=69%					
Test for overall effect: z=3.41, P<0.001					
Test for subgroup differences: χ^2=22.14, df=1, P<0.001, I^2=95.5%					

Fig 3 | Forest plot for a good functional outcome (modified Rankin scale core ≤2) at 90 days, including subgroup analysis by year of study publication. AIMT=adjunctive intra-arterial mechanical thrombectomy

Rodriguez FB *et al. BMJ*. 2016

ENCORE ?

2017 : Quel avenir pour la thrombolyse IV ?

REVIEW

Does the use of IV tPA in the current era of rapid and predictable recanalization by mechanical embolectomy represent good value?

Ronil V Chandra,[1,2] Thabele M Leslie-Mazwi,[3] Brijesh P Mehta,[4] Colin P Derdeyn,[5] Andrew M Demchuk,[6,7] Bijoy K Menon,[6,7] Mayank Goyal,[6,7] R Gilberto González,[8] Joshua A Hirsch[3]

J NeuroIntervent Surg. **2016**

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Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke

P. Yang, Yongwei Zhang, L. Zhang, Yongxin Zhang, K.M. Treurniet, W. Chen, Y. Peng, H. Han, J. Wang, S. Wang, C. Yin, S. Liu, P. Wang, Q. Fang, Hongchao Shi, J. Yang, C. Wen, C. Li, C. Jiang, J. Sun, X. Yue, M. Lou, M. Zhang, H. Shu, D. Sun, H. Liang, Tong Li, F. Guo, K. Ke, H. Yuan, G. Wang, W. Yang, Huaizhang Shi, Tianxiao Li, Z. Li, P. Xing, P. Zhang, Y. Zhou, H. Wang, Y. Xu, Q. Huang, T. Wu, R. Zhao, Q. Li, Y. Fang, Laixing Wang, J. Lu, Y. Li, J. Fu, X. Zhong, Y. Wang, Longde Wang, M. Goyal, D.W.J. Dippel, B. Hong, B. Deng, Y.B.W.E.M. Roos, C.B.L.M. Majoie, and J. Liu, for the DIRECT-MT Investigators*

Table 2. Trial Outcomes.*

Outcome	Endovascular Thrombectomy (N=327)	Alteplase with Endovascular Thrombectomy (N=329)	Measure of Effect	Adjusted Value (95% CI)
Primary outcome: modified Rankin Scale score at 90 days				
No. of patients with data	326	328		
Median score (IQR)	3 (2–5)	3 (2–5)	Common odds ratio	1.07 (0.81 to 1.40)
Secondary outcomes				
Clinical outcomes				
Modified Rankin scale score at 90 days according to range — no. (%)				
0 or 1	80 (24.5)	74 (22.5)	Odds ratio	1.09 (0.74 to 1.59)
0 to 2	119 (36.4)	121 (36.8)	Odds ratio	0.97 (0.68 to 1.37)
0 to 3	182 (55.7)	169 (51.4)	Odds ratio	1.25 (0.89 to 1.76)
0 to 4	218 (66.7)	207 (62.9)	Odds ratio	1.25 (0.88 to 1.77)
0 to 5	268 (82.0)	266 (80.9)	Odds ratio	1.10 (0.73 to 1.67)
Median NIHSS score (IQR)†				
After 24 hr	12 (5 to 20)	12 (5 to 22)	Beta coefficient	−0.52 (−2.13 to 1.09)
At 5–7 days or discharge	8 (2 to 16)	8 (2 to 19)	Beta coefficient	−1.26 (−3.20 to 0.68)
Barthel Index of 95 or 100 at 90 days — no./total no. (%)‡	156/326 (47.9)	151/328 (46.0)	Odds ratio	1.09 (0.78 to 1.53)
Median EQ-5D-5L score at 90 days (IQR)§	0.84 (0.48 to 0.95)	0.85 (0.26 to 1.00)	Beta coefficient	0.00 (−0.06 to 0.07)
Imaging outcomes				
Successful reperfusion before thrombectomy, as assessed on initial DSA — no. (%)¶	8 (2.4)	23 (7.0)	Odds ratio	0.33 (0.14 to 0.74)
eTICI score of 2b, 2c, or 3, as assessed on final angiogram — no./total no. (%)‖	243/306 (79.4)	267/316 (84.5)	Odds ratio	0.70 (0.47 to 1.06)
Recanalization at 24–72 hr, as assessed on CTA — no./total no. (%)**	240/282 (85.1)	245/275 (89.1)	Odds ratio	0.71 (0.42 to 1.20)
Median lesion volume on CT (IQR) — ml††	36.3 (9.8 to 114.8)	36.7 (9.6 to 99.2)	Beta coefficient	3.78 (−9.43 to 16.99)

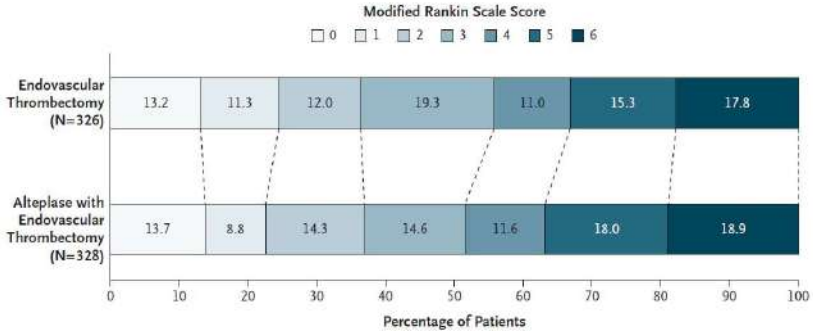

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Endovascular Thrombectomy (N=327)	Alteplase with Endovascular Thrombectomy (N=329)
Median age (IQR) — yr	69 (61–76)	69 (61–76)
Male sex — no. (%)	189 (57.8)	181 (55.0)
Median NIHSS score (IQR)†	17 (12–21)	17 (14–22)
Medical history — no. (%)		
Previous ischemic stroke	43 (13.1)	47 (14.3)
History of atrial fibrillation	152 (46.5)	149 (45.3)
History of diabetes mellitus	59 (18.0)	65 (19.8)
History of hypertension	193 (59.0)	201 (61.1)
Modified Rankin scale score of 1 or 2 before stroke onset — no. (%)‡	27 (8.3)	24 (7.3)
Median ASPECTS (IQR)§	9 (7–10)	9 (7–10)
Median systolic blood pressure at hospital arrival (IQR) — mm Hg	146 (130–163)	146 (131–161)
Median glucose level at hospital arrival (IQR) — mmol/liter¶	7.0 (5.8–8.6)	7.0 (5.9–8.8)
Cause of stroke — no. (%)‖		
Cardioembolism	146 (44.6)	144 (43.8)
Intracranial atherosclerosis	26 (8.0)	19 (5.8)
Ipsilateral extracranial ICA obstruction	34 (10.4)	29 (8.8)
Undetermined	121 (37.0)	137 (41.6)
Median duration (IQR) — min		
From stroke onset to randomization	167 (125–206)	177 (126–215)
From randomization to start of alteplase**	NA	7 (4–12)
From randomization to groin puncture††	31 (20–45)	36 (22–50.5)
From randomization to revascularization‡‡	102 (74–141)	96 (71.5–130.5)
From hospital admission to intravenous alteplase§§	NA	59 (45–78)
From hospital admission to groin puncture¶¶	84 (67–105)	85.5 (70–115)
Location of intracranial artery occlusion — no./total no. (%)‖‖		
Intracranial ICA	112/320 (35.0)	114/326 (35.0)
M1 middle cerebral artery segment	161/320 (50.3)	178/326 (54.6)
M2 middle cerebral artery segment	42/320 (13.1)	33/326 (10.1)

Research

JAMA | Original Investigation

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

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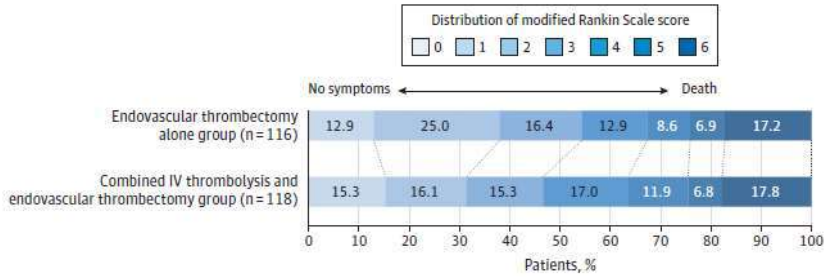
RESULTS The trial was stopped early because of efficacy when 234 of a planned 970 patients had undergone randomization. All 234 patients who were randomized (mean age, 68 years; 102 women [43.6%]) completed the trial. At the 90-day follow-up, 63 patients (54.3%) in the endovascular thrombectomy alone group vs 55 (46.6%) in the combined treatment group achieved functional independence at the 90-day follow-up (difference, 7.7%, 1-sided 97.5% CI, −5.1% to ∞)*P* for noninferiority = .003). No significant between-group differences were detected in symptomatic intracerebral hemorrhage (6.1% vs 6.8%; difference, −0.8%; 95% CI, −7.1% to 5.6%) and 90-day mortality (17.2% vs 17.8%; difference, −0.5%; 95% CI, −10.3% to 9.2%).



Shown are scores on the modified Rankin Scale for patients in each group who were evaluated by means of video (186 patients) and voice (6 patients) recordings and by local investigators (1 patient). Forty-one patients died before 90 days. IV indicates intravenous.

Table 1. Baseline Characteristics and Workflow Measures

	No. (%) of patients	
	Endovascular thrombectomy alone (n = 116)	Combined IV thrombolysis and endovascular thrombectomy (n = 118)
Demographic characteristics		
Age, median (IQR), y	70 (60-77)	70 (60-78)
Sex		
Men	66 (56.9)	66 (55.9)
Women	50 (43.1)	52 (44.1)
Medical history[a]		
Hypertension	69 (59.5)	74 (62.7)
Atrial fibrillation	62 (53.5)	62 (52.5)
Coronary heart disease[b]	30 (25.9)	19 (16.1)
Smoking[c]	28 (24.1)	29 (24.6)
Diabetes	25 (21.6)	20 (17.0)
Hyperlipidemia	18 (15.5)	22 (18.6)
Ischemic stroke	14 (12.1)	19 (16.1)
Prestroke score on the modified Rankin Scale of 1[d]	6 (5.2)	11 (9.3)
Stroke etiology		
Cardioembolism	65 (56.0)	69 (58.5)
Large artery atherosclerosis	32 (27.6)	28 (23.7)
Intracranial atherosclerosis	28 (24.1)	23 (19.5)
Unknown	15 (12.9)	20 (16.9)
Other[e]	4 (3.4)	1 (0.8)
Imaging characteristics[f]		
Baseline ASPECTS, No.[g]	115	117
Median (IQR)	8 (7-9)	8 (7-9)
Occlusion site on CT or MR angiography		
Intracranial internal carotid artery	18 (15.5)	17 (14.4)
M1 middle cerebral artery segment	95 (81.9)	99 (83.9)
M2 middle cerebral artery segment	3 (2.6)	2 (1.7)
Clinical examination at arrival, median (IQR)		
NIHSS score[h]	16 (12-20)	16 (13-20)
Systolic blood pressure, mm Hg[i]	146 (129-165)	145 (128-168)
Glucose level, mmol/L	6.7 (5.7-8.1)	6.9 (5.9-8.9)
No. of patients	114	115
Workflow times, median (IQR), min		
Onset to randomization[j]	170 (129-204)	168 (144-216)
Arrival to intravenous alteplase	NA	61 (49-81)
Arrival to arterial puncture	101 (80-135)	105 (80-132)
Onset to puncture[j]	200 (155-247)	210 (179-255)

Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial

*Serge Bracard, Xavier Ducrocq, Jean Louis Mas, Marc Soudant, Catherine Oppenheim, Thierry Moulin, Francis Guillemin, on behalf of the THRACE investigators**

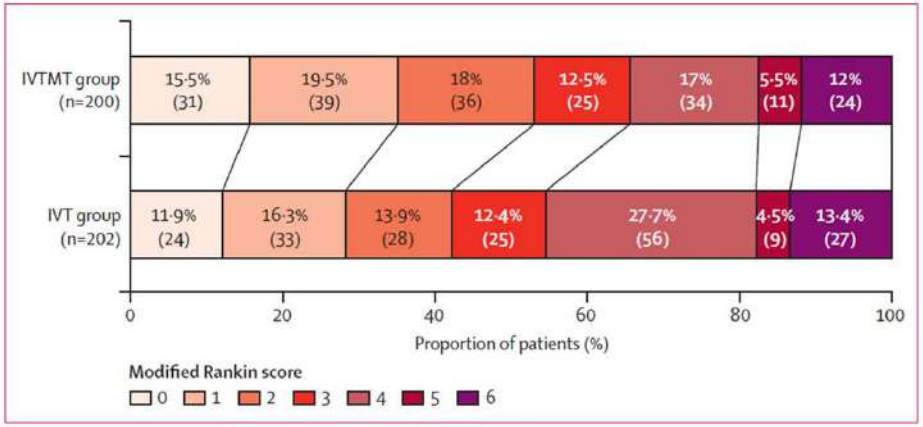


Figure 2: **Functional independence (modified Rankin score) at 3 months**
Data are proportion of patients (n). IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy.

Rankin ≤2: IV 42% *vs.* IVIA 53%

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

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Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Methods We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days in the pooled population and examine heterogeneity of this treatment effect across prespecified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome in the whole population (shift analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale score), site of occlusion (internal carotid artery *vs* M1 segment of middle cerebral artery *vs* M2 segment of middle cerebral artery), intravenous alteplase (yes *vs* no), baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Findings We analysed individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across prespecified subgroups for reduced disability ($p_{interaction}$=0·43). Effect sizes favouring endovascular thrombectomy over control were present in several strata of special interest, including in patients aged 80 years or older (cOR 3·68, 95% CI 1·95–6·92), those randomised more than 300 min after symptom onset (1·76, 1·05–2·97), and those not eligible for intravenous alteplase (2·43, 1·30–4·55). Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations.

Interpretation Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

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See **Comment** page 1695

Departments of Clinical Neuroscience and Radiology, Hotchkiss Brain Institute, Cummings School of Medicine, University of Calgary, Calgary, AB, Canada (Prof M Goyal MD, B K Menon MD, Prof A M Demchuk MD, Prof M D Hill MD); **Maastricht University Medical Center, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands** (W H van Zwam MD, D Beumer MD, Prof R J van Oostenbrugge MD); **Erasmus MC University Medical Center, Rotterdam, Netherlands** (Prof D W J Dippel MD, Prof A van der Lugt MD); **Department of Radiology** (Prof P J Mitchell MBBS) and **Department of Medicine and Neurology, Melbourne Brain Centre** (Prof S M Davis MD, B C V Campbell MD), **Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia; Hospital Germans Trias y Pujol, Barcelona, Spain** (Prof A Dávalos MD); **Academic Medical Center, Amsterdam, Netherlands** (Prof C B L M Majoie MD, Prof Y B W E M Roos MD, O A Berkhemer MD,

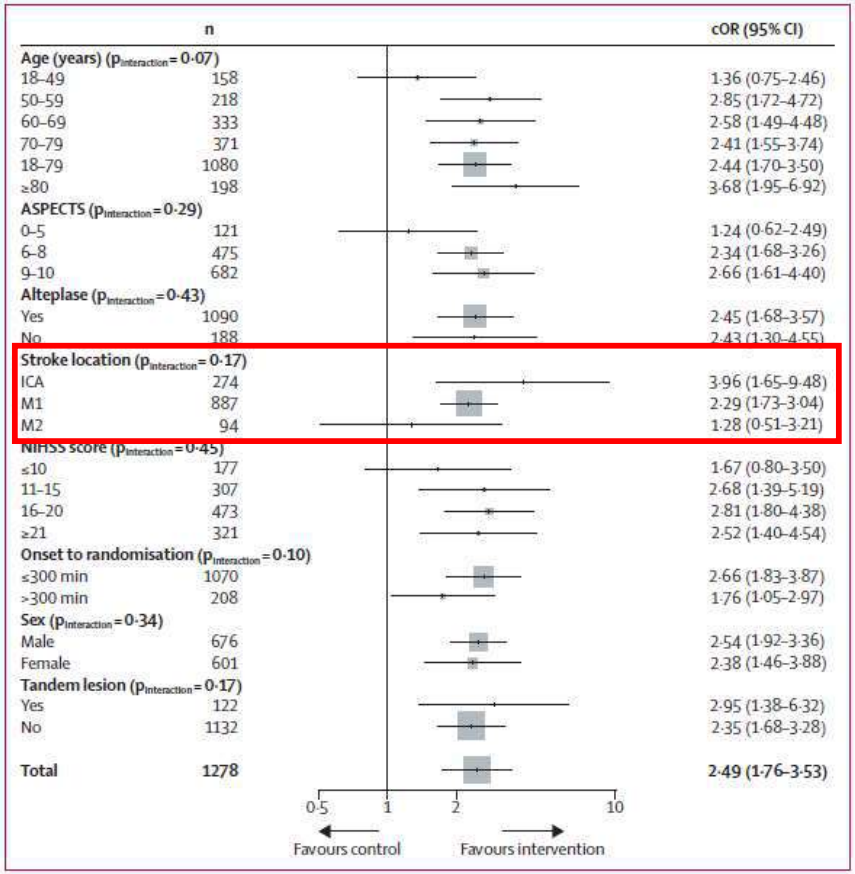


Figure 2: **Forest plot showing adjusted treatment effect for mRS at 90 days in prespecified subgroups with p values for heterogeneity across subgroups**
cOR=common odds ratio. mRS=modified Rankin Scale. ASPECTS=Alberta Stroke Program Early CT score. ICA=internal carotid artery. M1=M1 segment of middle cerebral artery. M2=M2 segment of middle cerebral artery. NIHSS=National Institutes of Health Stroke Scale.

Stroke
Volume 49, Issue 12, December 2018; Pages 2975-2982
https://doi.org/10.1161/STROKEAHA.118.022335

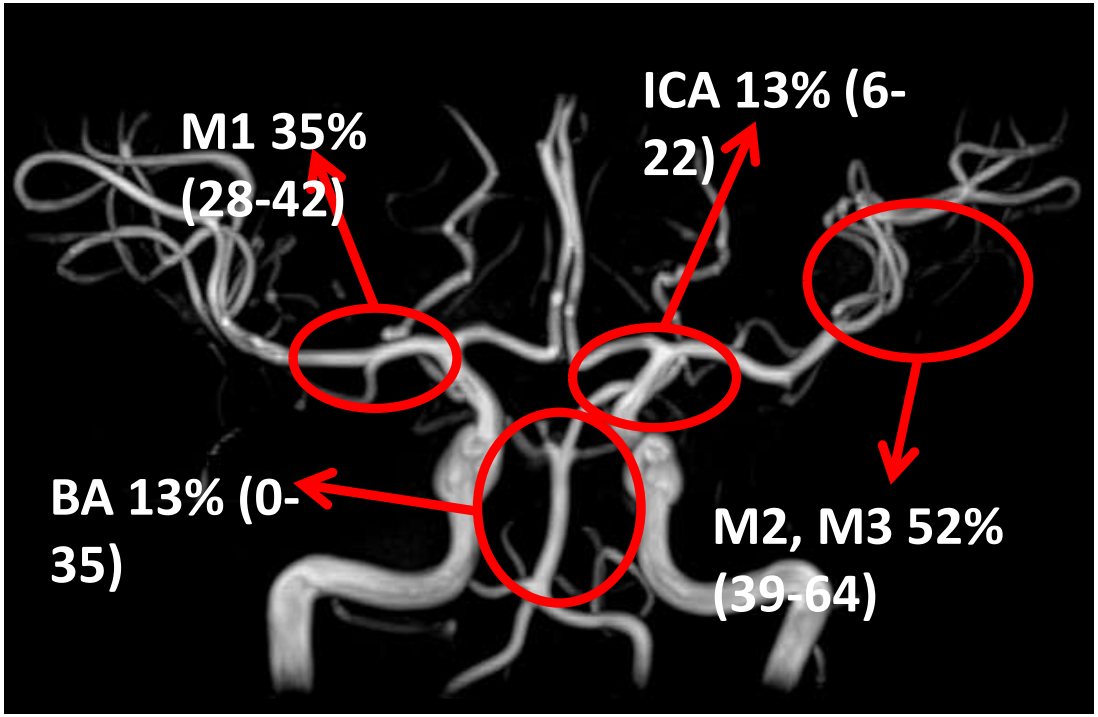
CLINICAL SCIENCES

Post-Thrombolysis Recanalization in Stroke Referrals for Thrombectomy

Incidence, Predictors, and Prediction Scores

Pierre Seners, MD, Guillaume Turc, PhD, Olivier Naggara, PhD, Hilde Henon, MD, Michel Piotin, PhD, Caroline Arquizan, MD, Tae-Hee Cho, PhD, Ana-Paula Narata, MD, Bertrand Lapergue, PhD, Sébastien Richard, PhD, Laurence Legrand, MD, Nicolas Bricout, MD, Raphaël Blanc, MD, Cyril Dargazanli, MD, Benjamin Gory, PhD, Séverine Debiais, MD, Marie Tisserand, PhD, Serge Bracard, PhD, Xavier Leclerc, PhD, Michael Obadia, MD, Vincent Costalat, PhD, Lise-Prune Berner, MD, Jean-Philippe Cottier, PhD, Arturo Consoli, MD, Xavier Ducrocq, PhD, Jean-Louis Mas, MD, Catherine Oppenheim, PhD*, Jean-Claude Baron, ScD*, on behalf of the PREDICT-RECANAL Collaborators, and PREDICT-RECANAL collaborators

≈20%



Stroke

BRIEF REPORT

Impact of Strategy on Clinical Outcome in Large Vessel Occlusion Stroke Successfully Reperfused: ETIS Registry Results

Marian Douarinou, MD; Benjamin Gory, PhD; Arturo Consoli, MSc; Bertrand Lapergue, PhD; Maeva Kyheng, BST; Julien Labreuche, BST; Mohammad Anadani, MD; Raphael Blanc, MSc; Gaultier Marnat, MD; Romain Bourcier, PhD; Igor Sibon, PhD; François Eugène, MD; Stéphane Vannier, MD; Gérard Audibert, PhD; Gioia Mione, MD; Sébastien Richard, PhD; on behalf of the ETIS Investigators*

Ne pas sous estimer la thrombolyse IV !!!

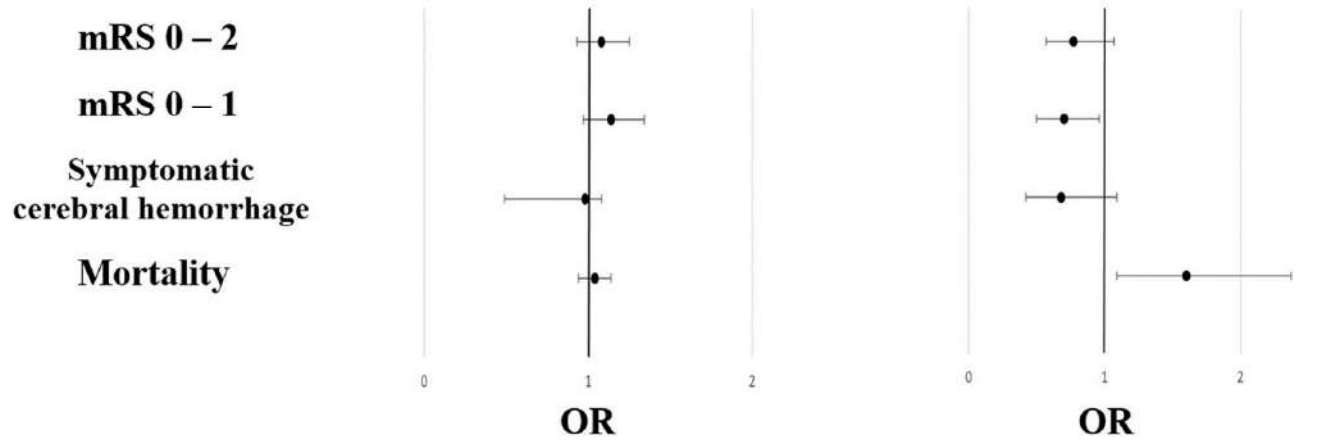
Effet sur la microcirculation

International meeting of the French society of neurology 2017

The next challenges for optimal reperfusion in the era of mechanical thrombectomy

M. Mazighi[a,b,c,d,e,*]

Impact of Strategy on Clinical Outcome in Large Vessel Occlusion Strokes Succesfully Reperfused: ETIS Registry Results.



JAMA | Original Investigation

Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke

The SKIP Randomized Clinical Trial

Kentaro Suzuki, MD, PhD; Yuji Matsumaru, MD, PhD; Masataka Takeuchi, MD; Masafumi Morimoto, MD, PhD; Ryuzaburo Kanazawa, MD, PhD; Yohei Takayama, MD; Yuki Kamiya, MD, PhD; Keigo Shigeta, MD, PhD; Seiji Okubo, MD, PhD; Mikito Hayakawa, MD; Norihiro Ishii, MD, PhD; Yorio Koguchi, MD, PhD; Tomoji Takigawa, MD, PhD; Masato Inoue, MD, PhD; Hiromichi Naito, MD; Takahiro Ota, MD, PhD; Teruyuki Hirano, MD, PhD; Noriyuki Kato, MD, PhD; Toshihiro Ueda, MD, PhD; Yasuyuki Iguchi, MD, PhD; Kazunori Akaji, MD, PhD; Wataro Tsuruta, MD, PhD; Kazunori Miki, MD, PhD; Shigeru Fujimoto, MD, PhD; Tetsuhiro Higashida, MD, PhD; Mitsuhiro Iwasaki, MD; Junya Aoki, MD, PhD; Yasuhiro Nishiyama, MD, PhD; Toshiaki Otsuka, MD, PhD; Kazumi Kimura, MD, PhD; for the SKIP Study Investigators

IMPORTANCE Whether intravenous thrombolysis is needed in combination with mechanical thrombectomy in patients with acute large vessel occlusion stroke is unclear.

OBJECTIVE To examine whether mechanical thrombectomy alone is noninferior to combined intravenous thrombolysis plus mechanical thrombectomy for favorable poststroke outcome.

DESIGN, SETTING, AND PARTICIPANTS Investigator-initiated, multicenter, randomized, open-label, noninferiority clinical trial in 204 patients with acute ischemic stroke due to large vessel occlusion enrolled at 23 hospital networks in Japan from January 1, 2017, to July 31, 2019, with final follow-up on October 31, 2019.

INTERVENTIONS Patients were randomly assigned to mechanical thrombectomy alone (n = 101) or combined intravenous thrombolysis (alteplase at a 0.6-mg/kg dose) plus mechanical thrombectomy (n = 103).

MAIN OUTCOMES AND MEASURES The primary efficacy end point was a favorable outcome defined as a modified Rankin Scale score (range, 0 [no symptoms] to 6 [death]) of 0 to 2 at 90 days, with a noninferiority margin odds ratio of 0.74, assessed using a 1-sided significance threshold of .025 (97.5% CI). There were 7 prespecified secondary efficacy end points, including mortality by day 90. There were 4 prespecified safety end points, including any intracerebral hemorrhage and symptomatic intracerebral hemorrhage within 36 hours.

RESULTS Among 204 patients (median age, 74 years; 62.7% men; median National Institutes of Health Stroke Scale score, 18), all patients completed the trial. Favorable outcome occurred in 60 patients (59.4%) in the mechanical thrombectomy alone group and 59 patients (57.3%) in the combined intravenous thrombolysis plus mechanical thrombectomy group, with no significant between-group difference (difference, 2.1% [1-sided 97.5% CI, −11.4% to ∞]; odds ratio, 1.09 [1-sided 97.5% CI, 0.63 to ∞]; $P = .18$ for noninferiority). Among the 7 secondary efficacy end points and 4 safety end points, 10 were not significantly different, including mortality at 90 days (8 [7.9%] vs 9 [8.7%]; difference, −0.8% [95% CI, −9.5% to 7.8%]; odds ratio, 0.90 [95% CI, 0.33 to 2.43]; $P > .99$). Any intracerebral hemorrhage was observed less frequently in the mechanical thrombectomy alone group than in the combined group (34 [33.7%] vs 52 [50.5%]; difference, −16.8% [95% CI, −32.1% to −1.6%]; odds ratio, 0.50 [95% CI, 0.28 to 0.88]; $P = .02$). Symptomatic intracerebral hemorrhage was not significantly different between groups (6 [5.9%] vs 8 [7.7%]; difference, −1.8% [95% CI, −9.7% to 6.1%]; odds ratio, 0.75 [95% CI, 0.25 to 2.24]; $P = .78$).

CONCLUSIONS AND RELEVANCE Among patients with acute large vessel occlusion stroke, mechanical thrombectomy alone, compared with combined intravenous thrombolysis plus mechanical thrombectomy, failed to demonstrate noninferiority regarding favorable functional outcome. However, the wide confidence intervals around the effect estimate also did not allow a conclusion of inferiority.

TRIAL REGISTRATION umin.ac.jp/ctr Identifier: UMIN000021488

JAMA. 2021;325(3):244-253. doi:10.1001/jama.2020.23522

Visual Abstract
Editorial page 229
Related article page 234
Supplemental content
CME Quiz at jamacmelookup.com

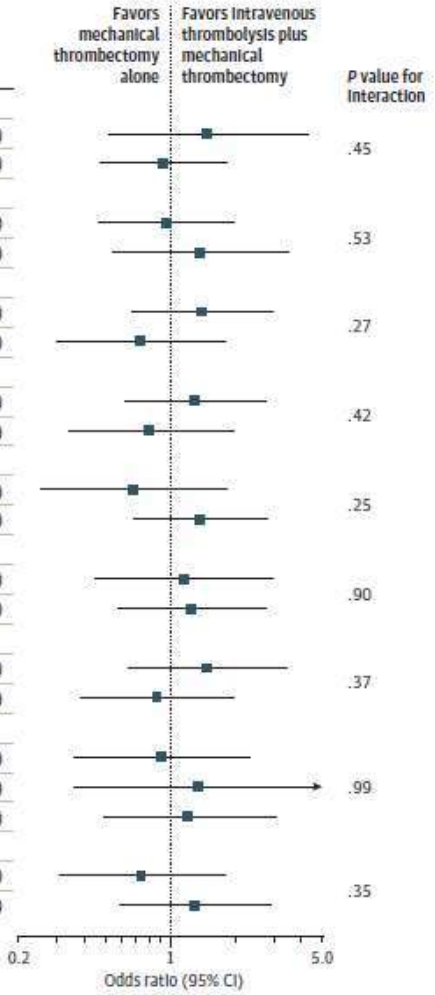
Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The SKIP Study Investigators are listed in the eAppendix in Supplement 3.

Corresponding Author: Kazumi Kimura, MD, PhD, Department of Neurology, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, 113-8602, Japan (k-kimura@nms.ac.jp).

Figure 3. Subgroup Plot Showing the Adjusted Treatment Effect for Favorable Outcome, With *P* Values for Heterogeneity Across Subgroups

	Mechanical thrombectomy alone (n = 101)	Intravenous thrombolysis plus mechanical thrombectomy (n = 103)	Odds ratio (95% CI)	*P* value for interaction
Age, y				
<70	24 (72.3)	21 (63.6)	1.52 (0.54-4.33)	.45
≥70	38 (52.9)	38 (54.3)	0.95 (0.49-1.85)	
Sex				
Male	33 (58.9)	43 (59.7)	0.97 (0.48-1.97)	.53
Female	27 (60.0)	16 (51.6)	1.41 (0.56-3.54)	
Atrial fibrillation				
Yes	36 (63.2)	35 (54.7)	1.42 (0.68-2.95)	.27
No	24 (54.6)	24 (61.5)	0.75 (0.31-1.80)	
Blood sugar, mg/dL				
<126	40 (65.6)	36 (59.0)	1.32 (0.63-2.76)	.42
≥126	20 (50.0)	23 (54.8)	0.83 (0.35-1.97)	
Use of antithrombotic agent				
Yes	16 (47.1)	18 (56.3)	0.69 (0.26-1.82)	.25
No	44 (65.7)	41 (57.8)	1.40 (0.70-2.79)	
NIHSS score at admission				
>5 and <18	30 (73.2)	37 (69.8)	1.18 (0.48-2.92)	.90
≥18	30 (50.0)	22 (44.0)	1.27 (0.60-2.70)	
ASPECTS				
>4 and <8	30 (56.6)	20 (46.5)	1.50 (0.67-3.37)	.37
≥8	30 (62.5)	39 (65.0)	0.90 (0.41-1.98)	
Occluded artery				
Internal carotid artery	21 (51.2)	19 (52.8)	0.94 (0.38-2.30)	.99
MI proximal	11 (57.9)	9 (50.0)	1.38 (0.38-5.03)	
MI distal	28 (68.3)	31 (63.3)	1.25 (0.52-3.01)	
Onset to randomization, min				
<120	34 (63.0)	31 (68.9)	0.77 (0.33-1.78)	.35
≥120	26 (55.3)	28 (48.3)	1.33 (0.61-2.87)	



Mean door-to-needle 50 min

SWIFT-DIRECT

Home

Home » The SWIFT DIRECT trial

The SWIFT DIRECT trial

Solitaire™ With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke (SWIFT DIRECT).

Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke.

Please find more information on www.clinicaltrials.gov

"Overall, it is extremely important to note that outcomes were very good in both treatment arms, with good functional outcomes—indicated by an mRS score from 0–2—of 62%," Fischer said. "In terms of the primary outcome, 57% of patients in the direct mechanical thrombectomy group had a good functional outcome, compared to 65% of patients in the bridging thrombolysis cohort." He went on to report a risk difference of -7.3% between the two groups, and a -15.1% lower limit of one-sided 95% confidence interval—which fell outside of the 12% non-inferiority margin, and led the researchers to conclude that SWIFT-DIRECT did not show statistical non-inferiority of direct mechanical thrombectomy when compared to IV t-PA plus thrombectomy.

NEWS • Conference News | ISC 2021

MR CLEAN-NO IV: No Advantage to Skipping tPA Before Stroke Thrombectomy

There may be scenarios where foregoing IV thrombolytics make sense, but most centers can stick with the guidelines, experts say.

by Todd Neale | MARCH 22, 2021

"The MR CLEAN-NO IV trial did not show any superiority nor noninferiority of direct endovascular treatment over the combination treatment with alteplase and endovascular treatment," Roos said, noting that hemorrhage rates also were similar in the two arms.

Guideline

EUROPEAN STROKE JOURNAL

European Stroke Journal
2022, Vol. 7(1) I–XXVI
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DOI: 10.1177/23969873221076968
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European Stroke Organisation – European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion

Guillaume Turc[1], Georgios Tsivgoulis[2,3], Heinrich J. Audebert[4], Hieronymus Boogaarts[5], Pervinder Bhogal[6], Gian Marco De Marchis[7], Ana Catarina Fonseca[8], Pooja Khatri[9], Mikaël Mazighi[10,11], Natalia Pérez de la Ossa[12], Peter D. Schellinger[13], Daniel Strbian[14], Danilo Toni[15], Philip White[16], William Whiteley[17], Andrea Zini[18], Wim van Zwam[19], and Jens Fiehler[20]

Abstract

Six randomized controlled clinical trials have assessed whether mechanical thrombectomy (MT) alone is non-inferior to intravenous thrombolysis (IVT) plus MT within 4.5 hours of symptom onset in patients with anterior circulation large vessel occlusion (LVO) ischaemic stroke and no contraindication to IVT. An expedited recommendation process was initiated by the European Stroke Organisation (ESO) and conducted with the European Society of Minimally Invasive Neurological Therapy (ESMINT) according to ESO standard operating procedure based on the GRADE system. We identified two relevant Population, Intervention, Comparator, Outcome (PICO) questions, performed systematic reviews and meta-analyses of the literature, assessed the quality of the available evidence and wrote evidence-based recommendations. Expert opinion was provided if insufficient evidence was available to provide recommendations based on the GRADE approach. For stroke patients with anterior circulation LVO directly admitted to a MT capable centre ('mothership') within 4.5 hours of symptom onset and eligible for both treatments, we recommend IVT plus MT over MT alone (moderate evidence, strong recommendation). MT should not prevent the initiation of IVT, nor should IVT delay MT. In stroke patients with anterior circulation LVO admitted to a centre without MT facilities and eligible for IVT ≤4.5 hrs and MT, we recommend IVT followed by rapid transfer to a MT capable-centre ('drip-and-ship') in preference to omitting IVT (low evidence, strong recommendation). Expert consensus statements on ischaemic stroke on awakening from sleep are also provided. Patients with anterior circulation LVO stroke should receive IVT in addition to MT if they have no contraindications to either treatment.

Keywords

ischaemic stroke, thrombolysis, thrombectomy, endovascular therapy, recommendations

TM+TIV vs TM alone

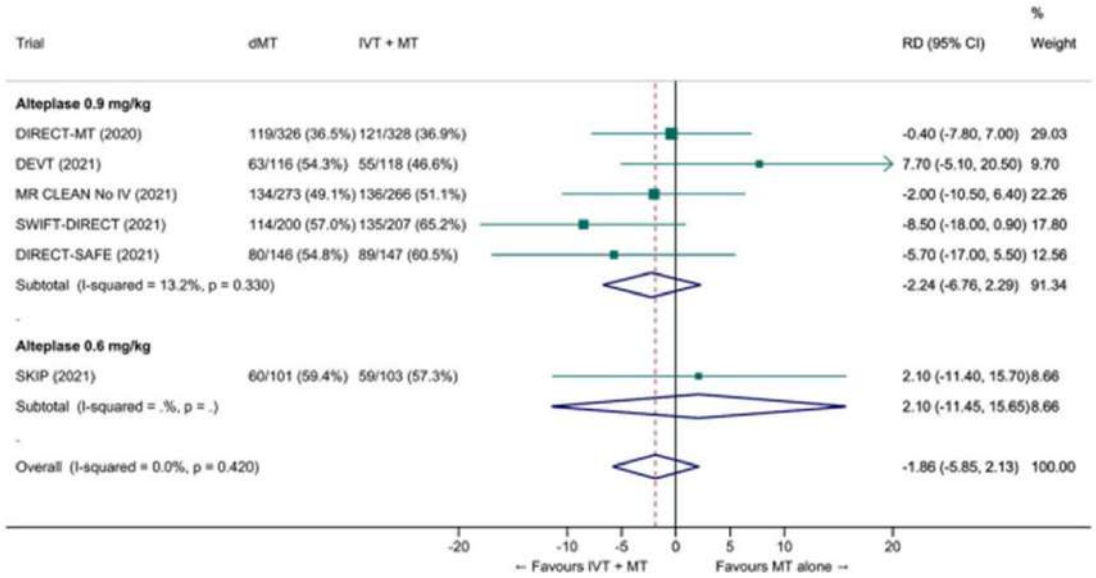


Figure 3. Pooled risk difference (in percent) for good outcome (mRS 0–2 at 90 days) in 'mothership' anterior circulation large vessel occlusion stroke patients treated with MT alone vs. IVT plus MT within 4.5 hrs of symptom onset (unadjusted pooled RD, random-effects meta-analysis). Abbreviations: dMT: direct mechanical thrombectomy (MT alone); IVT: intravenous thrombolysis with alteplase; MT: mechanical thrombectomy; RD: risk difference.

NON INFERIORITE NON DEMONTREE

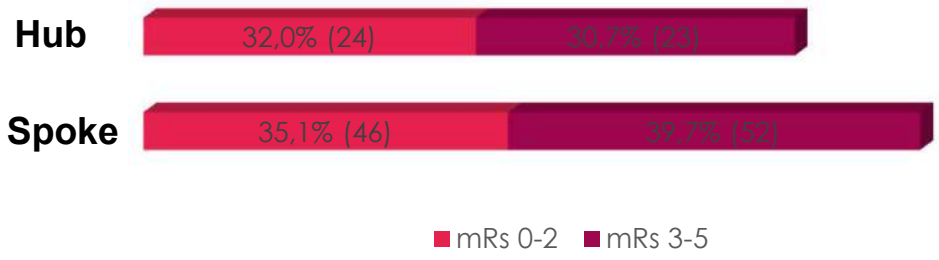
QUAND ?

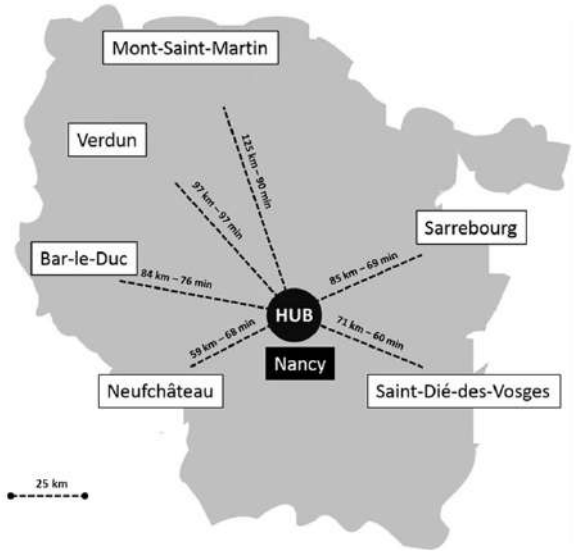
Outcome of Large Vessel Occlusion Stroke Patients after First Admission in Telestroke Spoke Versus Comprehensive Stroke Center

BMJ Journals
Journal of NeuroInterventional Surgery

CritR d'Inclusion	- Occlusion d'un gros tronc - Admission Hub vs Spoke - Dans les 6h - Quel que soit le TT final
CritR de Jugement I	**mRS 0-2 à 3 mois**

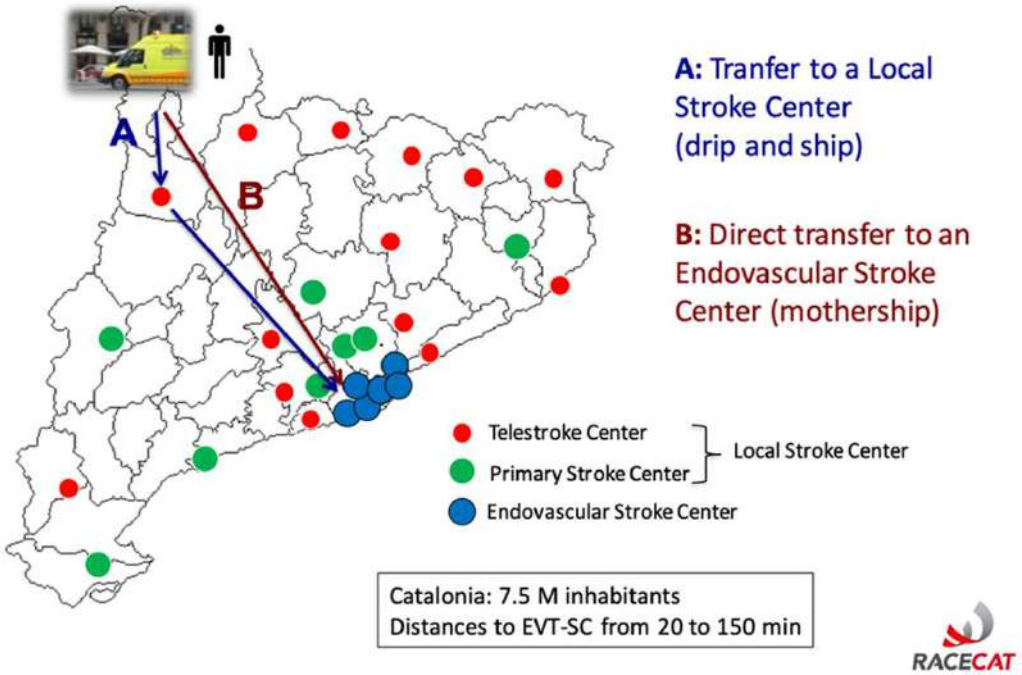
Résultats (n=207)	**Spoke (n=75)**	**Hub (n=132)**
TIV*	81%	54%
Délai TIV	171	166
TM*	27%	49%
Délai TM*	303 min	200 min





Distance moyenne : 87 km / 77 min

Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT) *ClinicalTrials.gov Identifier: NCT02795962*



The primary efficacy endpoint was comparable for both groups with an adjusted hazard ratio (aHR) of 1.02 in EVT-SC vs PSC. Good outcome (90-day mRS=0-2) was observed in 32.8% in PSC vs 33.4% in EVT-SC cohorts, while mortality (90-day mRS=6) was noted in 37.3% vs 35.8 %, respectively. The 90-day mRS shift analysis was also neutral, with an aHR of 0.965. When considering only patients with hemorrhagic stroke, the aHR for the mRS shift analysis at 90 days was 1.216, which was still insignificant (95% CI, 0.864 – 1.709). This included an increase in mortality among the EVT-SC cohort (48.6%) compared to PSC (40.7%).

PREhospital routage of acute STroke patients with suspected large vessel Occlusion: mothership *versus* drip and ship, a randomized control study in France (PRESTO-F)

Etude prospective, multicentrique, contrôlée, randomisée. N= 800

PREhospital routage of acute STroke patients with suspected large vessel Occlusion: mothership *versus* drip and ship, a randomized control study in France (PRESTO-F)

DRIP and SHIP *versus* MOTHERSHIP

Evaluation médico-économique d'une stratégie préhospitalière d'adressage direct vers un centre de recours avec neuroradiologie interventionnelle dans la prise en charge de l'AVC aigu. Essai multicentrique randomisé

R. Macrez[1,2,3], S. Baffert[4], H. Charreire[5], A. Bochaton[6], M. Mazighi[7], E. Roupie[1,8], E. Touzé[2,9]

(1) SAMU 14, Centre Hospitalier et Universitaire Caen, Caen, France.
(2) Normandie Université, Université Caen Normandie, Institut National de la Santé et de la Recherche Médicale U1237, Centre Hospitalier et Universitaire Caen, Caen, France.
(3) Département de traitements et d'accueil des urgences, Centre Hospitalier et Universitaire Caen, Caen, France.
(4) CEMKA, Bourg-la-Reine, France
(5) Département de Géographie, Université Paris-Est, Créteil, France
(6) Laboratoire LADYSS UMR7533, Université Paris Nanterre la Défense, Nanterre, France
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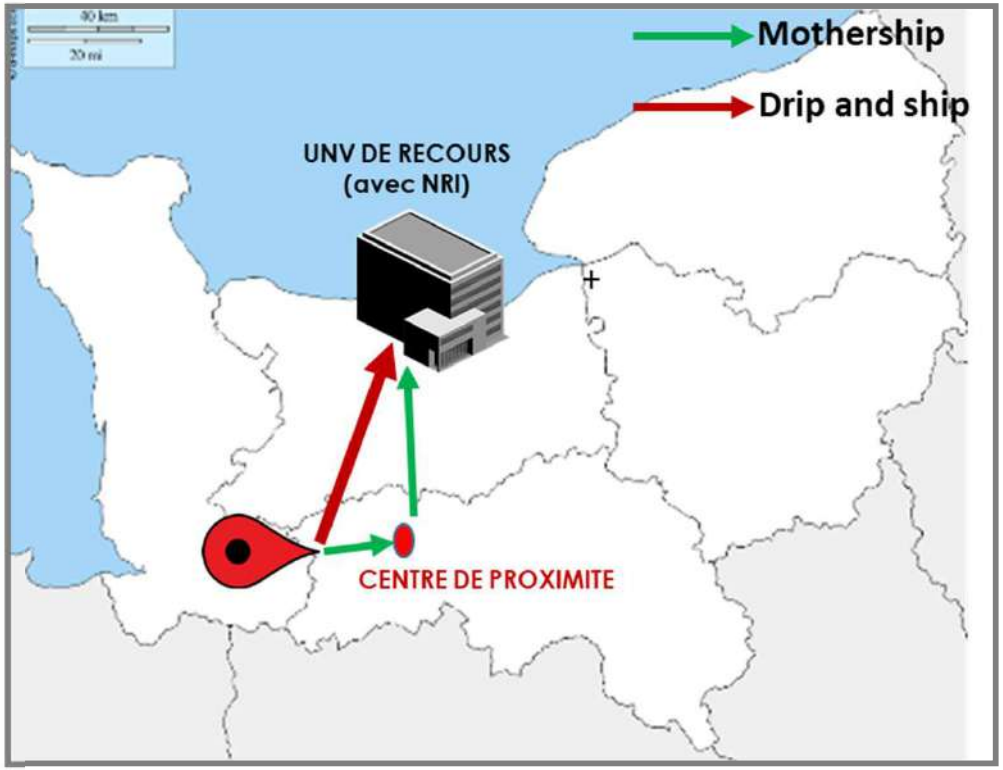


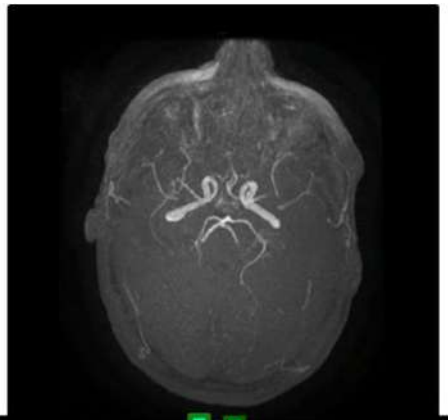
DAWN – DEFUSE 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*



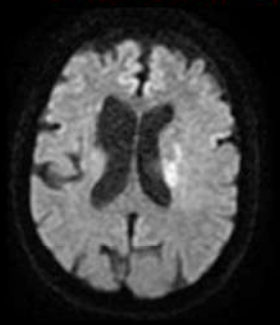
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

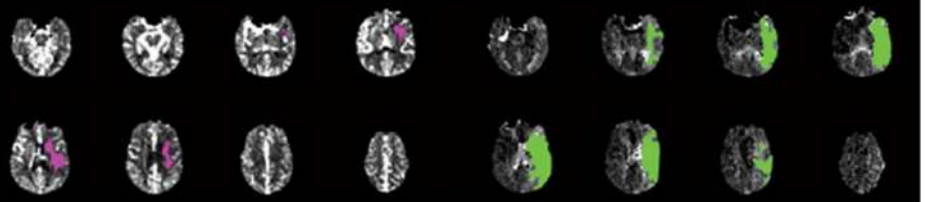
G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

Mismatch Radio/Clinique

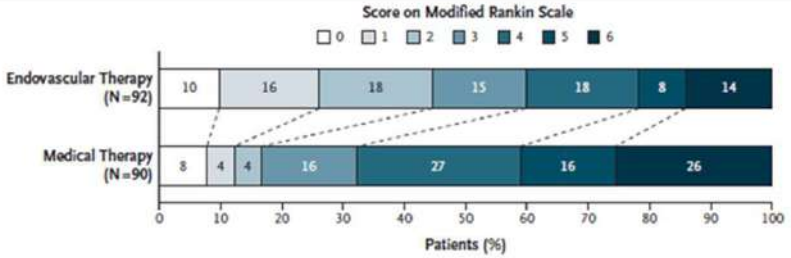


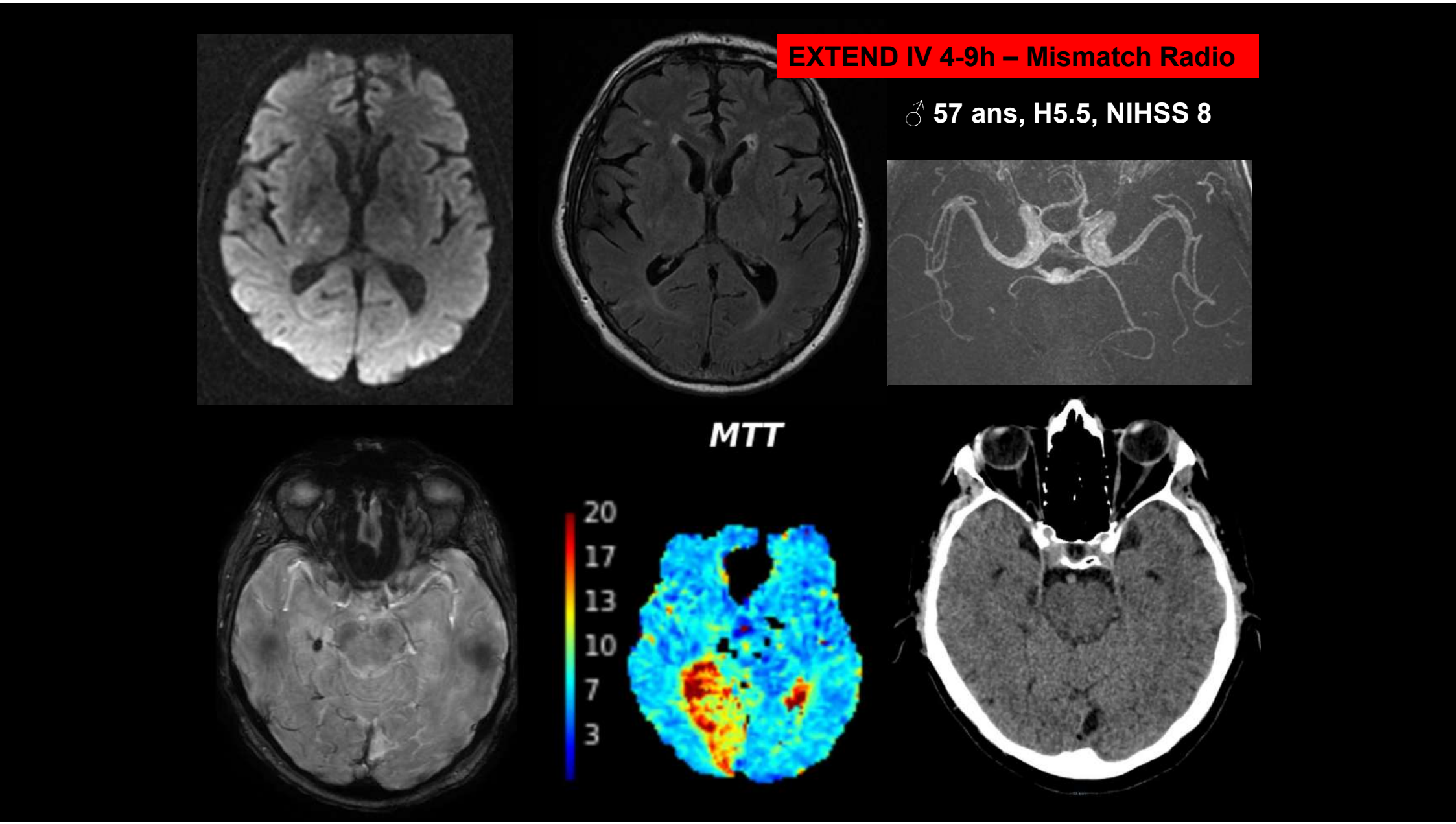
+ NIHSS > 10

Mismatch Infarctus/Perfusion

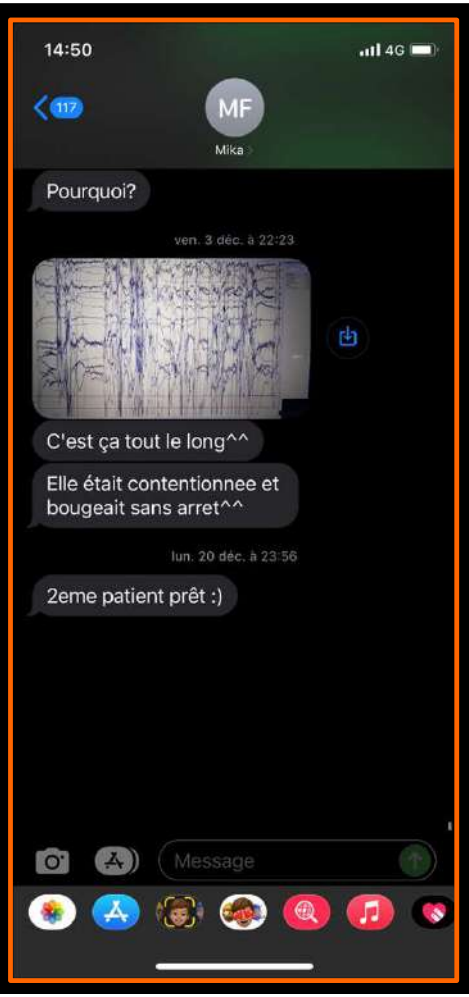


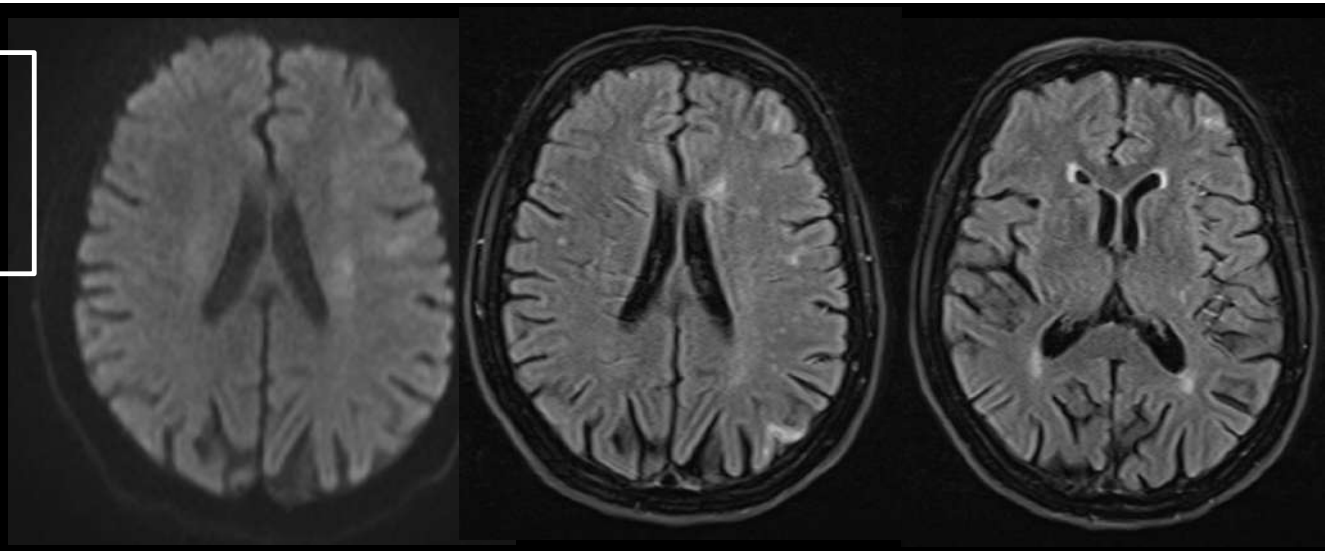
Infarctus < 70 mL **Infarctus/Oligémie > 1,8**

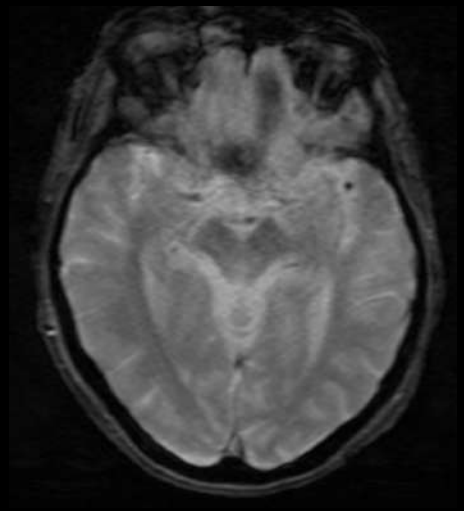


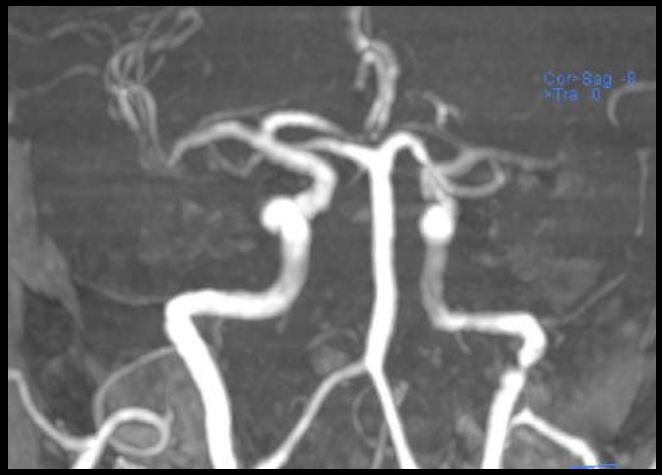

EXTEND IV 4-9h – Mismatch Radio
♂ 57 ans, H5.5, NIHSS 8
MTT
20
17
13
10
7
3

Mme P. Andrée 81 ans NIHSS10
Début symptômes 19h45
Fin de l'IRM 1h00 Mont-St-Martin (1h30 de TM)
Pas d'anticoagulant ni antiplaquettaires









N=543 patients
Diagnostic infarctus < 4,5 heures
Se=62%, Sp=78%

Accord inter observateur
FLAIR +/- : 78% des cas

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Identification of patients within 4·5 h of symptom onset				
DWI-positive (n=516)	62% (57–67)	78% (72–84)	83% (79–88)	54% (48–60)
MCA (n=469)	63% (57–68)	79% (37–86)	85% (80–90)	53% (47–60)
MCA+NIHSS >3 (n=408)	64% (58–70)	81% (74–87)	87% (81–91)	53% (46–60)
MCA+DWI lesion >5 mL (n=280)	58% (51–66)	84% (75–90)	86% (78–91)	55% (47–63)
Identification of patients within 6 h of symptom onset				
DWI-positive (n=516)	56% (51–61)	87% (80–93)	93% (91–97)	34% (28–39)
MCA (n=469)	56% (51–61)	87% (80–94)	95% (92–98)	33% (27–39)
MCA+NIHSS >3 (n=408)	57% (52–62)	88% (78–94)	95% (92–98)	32% (25–39)
MCA+DWI lesion >5 mL (n=280)	52% (45–59)	92% (82–97)	96% (90–99)	34% (27–42)

DWI=diffusion-weighted imaging. PPV=positive predictive value. NPV=negative predictive value. MCA=middle cerebral artery. NIHSS=National Institutes of Health Stroke Scale.

Table 4: **Predictive values of DWI-FLAIR mismatch for the identification of patients within either 4·5 h or 6 h of symptom onset**

DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study

Götz Thomalla, Bastian Cheng, Martin Ebinger, Qing Hao, Thomas Tourdias, Ona Wu, Jong S Kim, Lorenz Breuer, Oliver C Singer, Steven Warach, Soren Christensen, Andras Treszl, Nils D Forkert, Ivana Galinovic, Michael Rosenkranz, Tobias Engelhorn, Martin Köhrmann, Matthias Endres, Dong-Wha Kang, Vincent Dousset, A Gregory Sorensen, David S Liebeskind, Jochen B Fiebach, Jens Fiehler, Christian Gerloff, for the STIR and VISTA Imaging Investigators

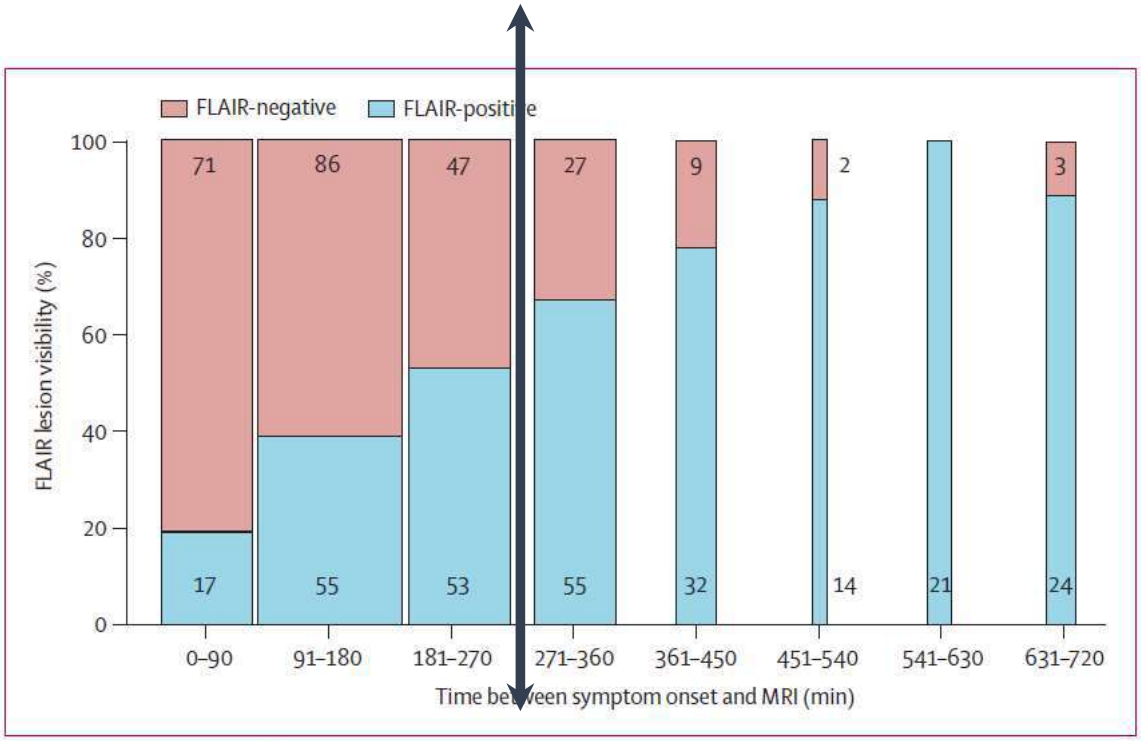


Figure 3: **FLAIR lesion visibility in relation to time from symptom onset**
Visibility of acute ischaemic lesions on FLAIR images in relation to time from symptom onset. Numbers are patients within each time interval, which also relate to the widths of the columns. FLAIR=fluid-attenuated inversion recovery.

WAKE-UP

The NEW ENGLAND JOURNAL of MEDICINE

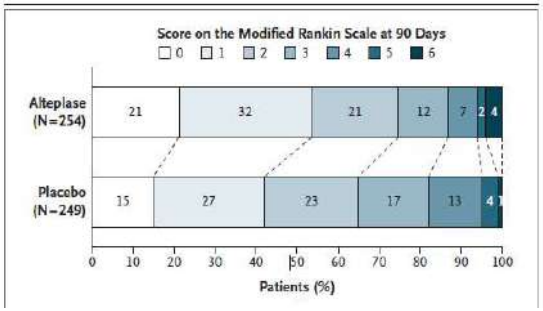
ESTABLISHED IN 1812 AUGUST 16, 2018 VOL. 379 NO. 7

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

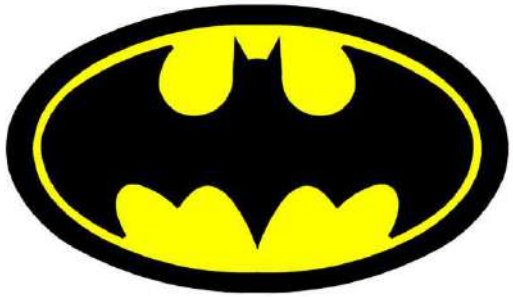
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Alteplase Group (N=254)	Placebo Group (N=249)
Mean age ±SD — yr	65.3±11.2	65.2±11.9
Male sex — no. (%)	165 (65.0)	160 (64.3)
Reason for unknown time of symptom onset — no. (%)		
Nighttime sleep	227 (89.4)	222 (89.2)
Daytime sleep	12 (4.7)	11 (4.4)
Aphasia, confusion, or other	15 (5.9)	16 (6.4)
Median interval between last time the patient was known to be well and symptom recognition (IQR) — hr	7.2 (4.7–8.7)	7.0 (5.0–9.0)
Medical history — no. (%)		
Arterial hypertension	135 (53.1)	131 (52.6)
Diabetes mellitus	43 (16.9)	39 (15.7)
Hypercholesterolemia	93 (36.6)	85 (34.1)
Atrial fibrillation	30 (11.8)	29 (11.6)
History of ischemic stroke	37 (14.6)	31 (12.4)
Median NIHSS score (IQR)†	6 (4–9)	6 (4–9)
Vessel occlusion on time-of-flight MRA — no./total no. (%)		
Any	84/249 (33.7)	84/246 (34.1)
Intracranial internal carotid artery	24/249 (9.6)	11/246 (4.5)
Middle cerebral artery main stem	35/249 (14.1)	37/246 (15.0)
Middle cerebral artery branch	32/249 (12.9)	36/246 (14.6)
Other‡	12/249 (4.8)	12/246 (4.9)
Median lesion volume on diffusion-weighted imaging (IQR) — ml	2.0 (0.8–7.9)	2.5 (0.7–8.8)
Median time from symptom recognition to MRI (IQR) — hr	2.6 (1.9–3.3)	2.6 (2.1–3.3)
Median time between end of MRI and treatment initiation (IQR) — min	25 (16–35)	26 (18–37)
Median time from symptom recognition to treatment initiation (IQR) — hr	3.1 (2.5–3.8)	3.2 (2.6–3.9)
Interval between last time that the patient was last known to be well and treatment initiation (IQR) — hr	10.3 (8.1–12.0)	10.4 (8.1–12.1)



mRS 0-1 : + 11%

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03



DESMOTEPLASE – Les essais DIAS

DIAS 1,2, DEDAS : Mismatch Diff/Perf > 20%
DIAS 3,4 et DIAS J : Occlusion intracrânienne Vol < 1/3 ACM, ½ ACA ou ACP
3-9h

REPERFUSION

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 subgruop<90ug/kg						
DIAS 2001	3	13	2	10	3.4%	1.20 [0.16, 9.01]
Subtotal (95% CI)		**13**		**10**	**3.4%**	**1.20 [0.16, 9.01]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
5.1.2 subgruop=90ug/kg						
DEDAS 2003	2	11	3	8	5.5%	0.37 [0.05, 3.01]
DIAS 2001	7	15	2	10	2.5%	3.50 [0.55, 22.30]
DIAS-3 2009	76	156	63	151	64.1%	1.33 [0.85, 2.08]
DIAS-4 2014	25	48	17	58	14.4%	2.62 [1.18, 5.84]
DIAS-J 2010	6	13	5	13	5.3%	1.37 [0.29, 6.53]
Subtotal (95% CI)		**243**		**240**	**91.7%**	**1.53 [1.07, 2.21]**
Total events	116		90			
Heterogeneity: Chi^2 = 4.67, df = 4 (P = 0.32); I^2 = 14%						
Test for overall effect: Z = 2.31 (P = 0.02)						
5.1.3 subgruop=125ug/kg						
DEDAS 2003	8	15	3	8	3.6%	1.90 [0.33, 11.01]
DIAS 2001	10	14	2	10	1.3%	10.00 [1.44, 69.26]
Subtotal (95% CI)		**29**		**18**	**4.9%**	**4.07 [1.16, 14.24]**
Total events	18		5			
Heterogeneity: Chi^2 = 1.55, df = 1 (P = 0.21); I^2 = 35%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**285**		**268**	**100.0%**	**1.65 [1.17, 2.32]**
Total events	137		97			
Heterogeneity: Chi^2 = 8.27, df = 7 (P = 0.31); I^2 = 15%						
Test for overall effect: Z = 2.85 (P = 0.004)						
Test for subgroup differences: Chi^2 = 2.24, df = 2 (P = 0.33), I^2 = 10.9%						

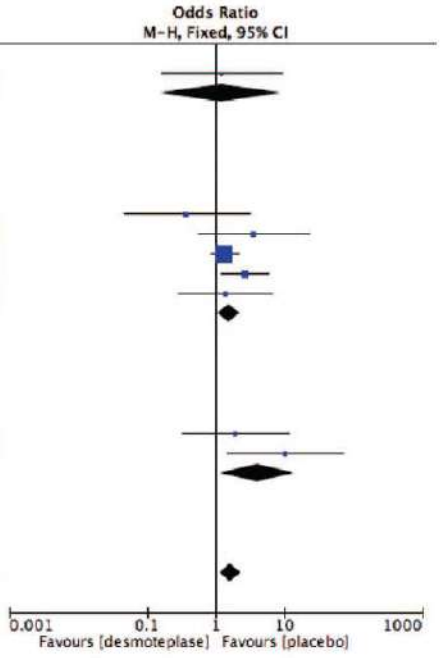
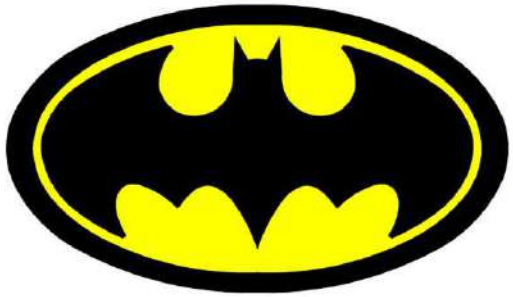


Figure 11. Forest plot of reperfusion outcome data for the desmoteplase subgroup and placebo group.



DESMOTEPLASE – Les essais DIAS

DIAS 1,2, DEDAS : Mismatch Diff/Perf > 20%
DIAS 3,4 et DIAS J : Occlusion intracrânienne Vol < 1/3 ACM, ½ ACA ou ACP
3-9h

HEMORRAGIE

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 subgroup<90ug/kg						
DIAS 2001	0	15	0	11		Not estimable
DIAS-J 2010	1	16	2	16	13.9%	0.47 [0.04, 5.73]
Subtotal (95% CI)		**31**		**27**	**13.9%**	**0.47 [0.04, 5.73]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.1.2 subgroup=90ug/kg						
DEDAS 2003	0	14	0	8		Not estimable
DIAS 2001	1	15	0	11	3.8%	2.38 [0.09, 64.05]
DIAS-2 2005	2	57	0	63	3.4%	5.72 [0.27, 121.72]
DIAS-3 2009	6	240	5	238	36.4%	1.19 [0.36, 3.97]
DIAS-4 2014	6	126	3	131	20.8%	2.13 [0.52, 8.72]
DIAS-J 2010	0	16	2	16	18.0%	0.18 [0.01, 3.97]
Subtotal (95% CI)		**468**		**467**	**82.5%**	**1.45 [0.67, 3.11]**
Total events	15		10			
Heterogeneity: Chi^2 = 3.01, df = 4 (P = 0.56); I^2 = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.1.3 subgroup=125ug/kg						
DEDAS 2003	0	15	0	8		Not estimable
DIAS 2001	0	15	0	11		Not estimable
DIAS-2 2005	3	66	0	63	3.6%	7.00 [0.35, 138.30]
Subtotal (95% CI)		**96**		**82**	**3.6%**	**7.00 [0.35, 138.30]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**595**		**576**	**100.0%**	**1.51 [0.76, 3.01]**
Total events	19		12			
Heterogeneity: Chi^2 = 4.87, df = 6 (P = 0.56); I^2 = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi^2 = 1.85, df = 2 (P = 0.40), I^2 = 0%						

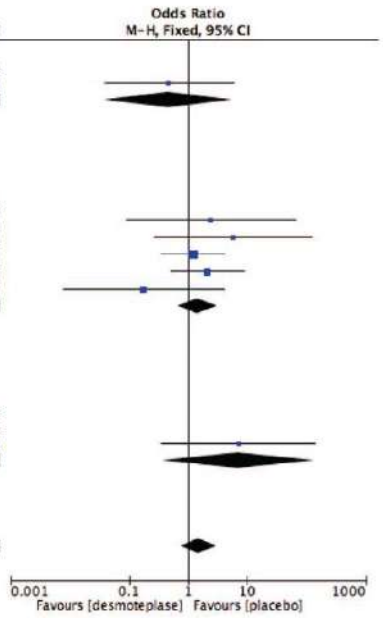
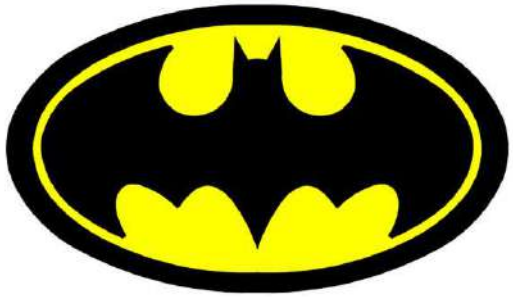


Figure 7. Forest plot of symptomatic intracranial hemorrhage outcome data for the desmoteplase subgroups and placebo group.



DESMOTEPLASE – Les essais DIAS

DIAS 1,2, DEDAS : Mismatch Diff/Perf > 20%
DIAS 3,4 et DIAS J : Occlusion intracrânienne Vol < 1/3 ACM, ½ ACA ou ACP
3-9h

PRONOSTIC

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 subgroup<90ug/kg						
DIAS 2001	2	15	2	11	1.7%	0.69 [0.08, 5.86]
Subtotal (95% CI)		**15**		**11**	**1.7%**	**0.69 [0.08, 5.86]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
3.1.2 subgroup=90ug/kg						
DEDAS 2003	4	14	2	8	1.5%	1.20 [0.17, 8.66]
DIAS 2001	7	15	2	11	1.0%	3.94 [0.63, 24.73]
DIAS-2 2005	27	57	29	63	12.2%	1.06 [0.51, 2.16]
DIAS-3 2009	108	236	100	237	45.4%	1.16 [0.80, 1.66]
DIAS-4 2014	40	124	37	128	20.7%	1.17 [0.68, 2.00]
Subtotal (95% CI)		**446**		**447**	**80.8%**	**1.18 [0.90, 1.55]**
Total events	186		170			
Heterogeneity: Chi^2 = 1.76, df = 4 (P = 0.78); I^2 = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
3.1.3 subgroup=125ug/kg						
DEDAS 2003	9	15	2	8	0.9%	4.50 [0.67, 30.23]
DIAS 2001	9	15	2	11	0.8%	6.75 [1.06, 42.84]
DIAS-2 2005	24	66	29	63	15.8%	0.67 [0.33, 1.36]
Subtotal (95% CI)		**96**		**82**	**17.5%**	**1.13 [0.63, 2.04]**
Total events	42		33			
Heterogeneity: Chi^2 = 7.73, df = 2 (P = 0.02); I^2 = 74%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**557**		**540**	**100.0%**	**1.16 [0.91, 1.49]**
Total events	230		205			
Heterogeneity: Chi^2 = 9.76, df = 8 (P = 0.28); I^2 = 18%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi^2 = 0.25, df = 2 (P = 0.88), I^2 = 0%						

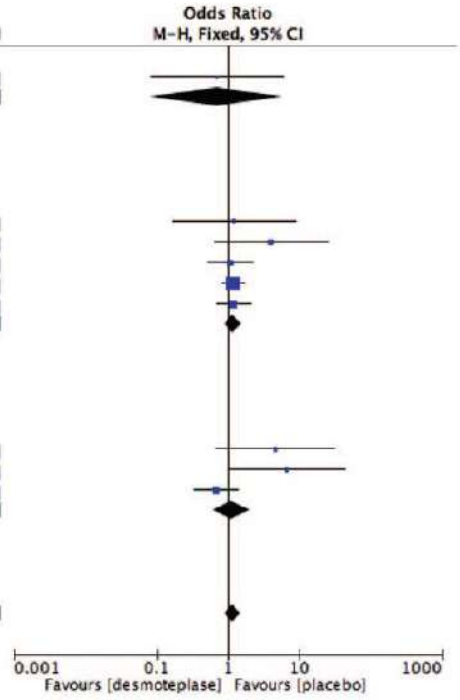


Figure 10. Forest plot of good clinical outcome at 90 days outcome data for the desmoteplase subgroup and placebo group.

IST-3

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial *Lancet* 2012

*The IST-3 collaborative group**

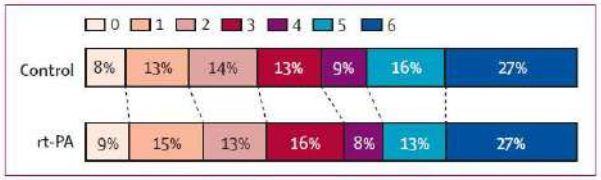


Figure 2: Outcome at 6 months: Oxford Handicap Scale (OHS) by treatment group

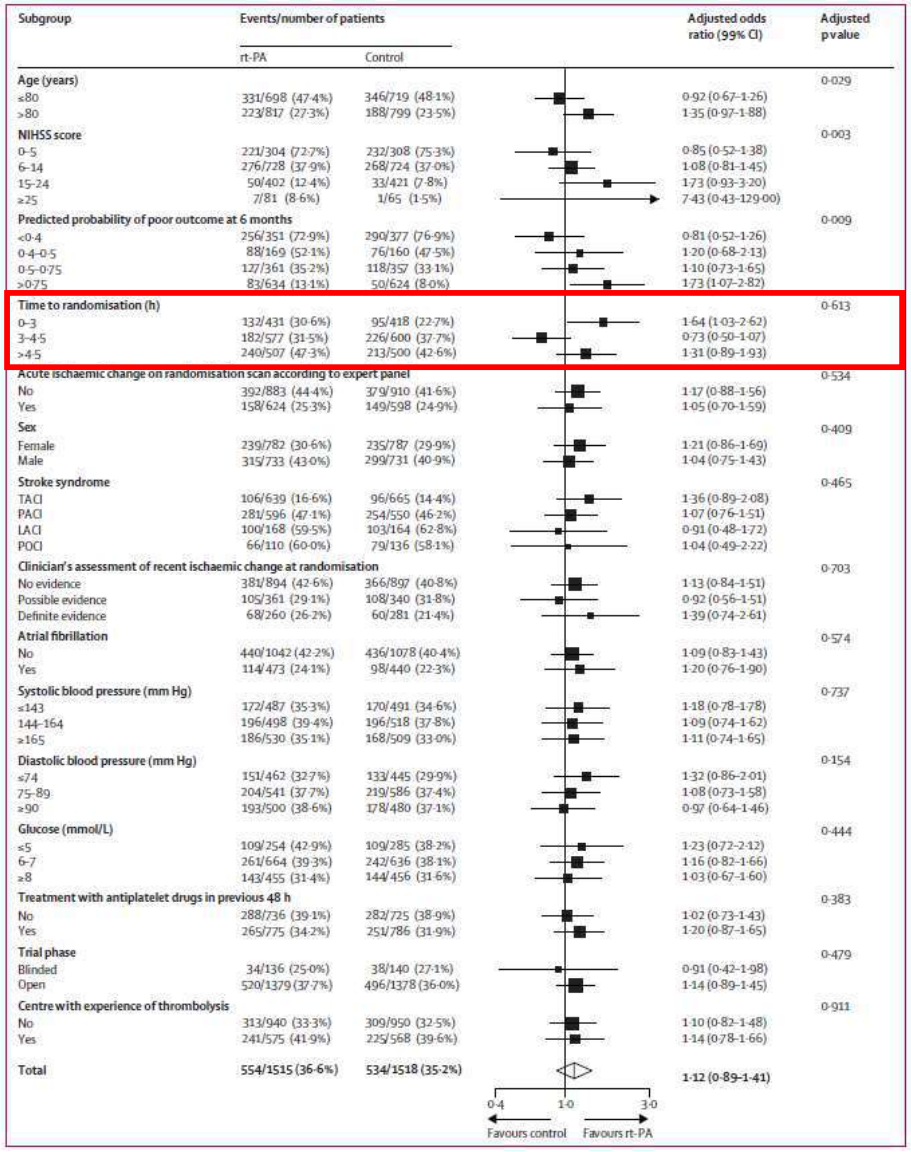
For the ordinal analysis, which was adjusted for age, National Institutes of Health Stroke Scale (NIHSS), delay (all linear), and and presence or absence of visible acute ischaemic change on baseline scan as judged by the expert reader, the statistical analysis plan prespecified that OHS levels 4, 5, and 6 were grouped and 0, 1, 2, 3 remained discrete. In that analysis, the common odds ratio was 1·27 (95% CI 1·10–1·47; p=0·001). An ordinal analysis with OHS levels 0, 1, 2, 3, 4, 5, and 6 all discrete, adjusted in the same way, gave an odds ratio of 1·17 (95% CI 1·03–1·33; p=0·016). rt-PA=recombinant tissue plasminogen activator.

53% patients ≥ 80 ans avec TIV <u>dans les 6H</u>

Imagerie qui élimine hémorragie

Effet + en analyse ordinale

7% HCS



Subgroup	Events/number of patients		Adjusted odds ratio (99% CI)	Adjusted p value
	rt-PA	Control		
Age (years)				0·029
≤80	331/698 (47·4%)	346/719 (48·1%)	0·92 (0·67–1·26)	
>80	223/817 (27·3%)	188/799 (23·5%)	1·35 (0·97–1·88)	
NIHSS score				0·003
0–5	221/304 (72·7%)	232/308 (75·3%)	0·85 (0·52–1·38)	
6–14	276/728 (37·9%)	268/724 (37·0%)	1·08 (0·81–1·45)	
15–24	50/402 (12·4%)	33/421 (7·8%)	1·73 (0·93–3·20)	
≥25	7/81 (8·6%)	1/65 (1·5%)	7·43 (0·43–129·00)	
Predicted probability of poor outcome at 6 months				0·009
<0·4	256/351 (72·9%)	290/377 (76·9%)	0·81 (0·52–1·26)	
0·4–0·5	88/169 (52·1%)	76/160 (47·5%)	1·20 (0·68–2·13)	
0·5–0·75	127/361 (35·2%)	118/357 (33·1%)	1·10 (0·73–1·65)	
>0·75	83/634 (13·1%)	50/624 (8·0%)	1·73 (1·07–2·82)	
Time to randomisation (h)				0·613
0–3	132/431 (30·6%)	95/418 (22·7%)	1·64 (1·03–2·62)	
3–4·5	182/577 (31·5%)	226/600 (37·7%)	0·73 (0·50–1·07)	
>4·5	240/507 (47·3%)	213/500 (42·6%)	1·31 (0·89–1·93)	
Acute ischaemic change on randomisation scan according to expert panel				0·534
No	392/883 (44·4%)	379/910 (41·6%)	1·17 (0·88–1·56)	
Yes	158/624 (25·3%)	149/598 (24·9%)	1·05 (0·70–1·59)	
Sex				0·409
Female	239/782 (30·6%)	235/787 (29·9%)	1·21 (0·86–1·69)	
Male	315/733 (43·0%)	299/731 (40·9%)	1·04 (0·75–1·43)	
Stroke syndrome				0·465
TACI	106/639 (16·6%)	96/665 (14·4%)	1·36 (0·89–2·08)	
PACI	281/596 (47·1%)	254/550 (46·2%)	1·07 (0·76–1·51)	
LACI	100/168 (59·5%)	103/164 (62·8%)	0·91 (0·48–1·72)	
POCI	66/110 (60·0%)	79/136 (58·1%)	1·04 (0·49–2·22)	
Clinician's assessment of recent ischaemic change at randomisation				0·703
No evidence	381/894 (42·6%)	366/897 (40·8%)	1·13 (0·84–1·51)	
Possible evidence	105/361 (29·1%)	108/340 (31·8%)	0·92 (0·56–1·51)	
Definite evidence	68/260 (26·2%)	60/281 (21·4%)	1·39 (0·74–2·61)	
Atrial fibrillation				0·574
No	440/1042 (42·2%)	436/1078 (40·4%)	1·09 (0·83–1·43)	
Yes	114/473 (24·1%)	98/440 (22·3%)	1·20 (0·76–1·90)	
Systolic blood pressure (mm Hg)				0·737
≤143	172/487 (35·3%)	170/491 (34·6%)	1·18 (0·78–1·78)	
144–164	196/498 (39·4%)	196/518 (37·8%)	1·09 (0·74–1·62)	
>165	186/530 (35·1%)	168/509 (33·0%)	1·11 (0·74–1·65)	
Diastolic blood pressure (mm Hg)				0·154
≤74	151/462 (32·7%)	133/445 (29·9%)	1·32 (0·86–2·01)	
75–89	204/541 (37·7%)	219/586 (37·4%)	1·08 (0·73–1·58)	
≥90	193/500 (38·6%)	178/480 (37·1%)	0·97 (0·64–1·46)	
Glucose (mmol/L)				0·444
≤5	109/254 (42·9%)	109/285 (38·2%)	1·23 (0·72–2·12)	
6–7	261/664 (39·3%)	242/636 (38·1%)	1·16 (0·82–1·66)	
≥8	143/455 (31·4%)	144/456 (31·6%)	1·03 (0·67–1·60)	
Treatment with antiplatelet drugs in previous 48 h				0·383
No	288/736 (39·1%)	282/725 (38·9%)	1·02 (0·73–1·43)	
Yes	265/775 (34·2%)	251/786 (31·9%)	1·20 (0·87–1·65)	
Trial phase				0·479
Blinded	34/136 (25·0%)	38/140 (27·1%)	0·91 (0·42–1·98)	
Open	520/1379 (37·7%)	496/1378 (36·0%)	1·14 (0·89–1·45)	
Centre with experience of thrombolysis				0·911
No	313/940 (33·3%)	309/950 (32·5%)	1·10 (0·82–1·48)	
Yes	241/575 (41·9%)	225/568 (39·6%)	1·14 (0·78–1·66)	
Total	**554/1515 (36·6%)**	**534/1518 (35·2%)**	**1·12 (0·89–1·41)**	

Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial

EPITHET

Lancet Neurol 2008

*Stephen M Davis, *Geoffrey A Donnan, Mark W Parsons, Christopher Levi, Kenneth S Butcher, Andre Peeters, P Alan Barber, Christopher Bladin, Deidre A De Silva, Graham Byrnes, Jonathan B Chalk, John N Fink, Thomas E Kimber, David Schultz, Peter J Hand, Judith Frayne, Graeme Hankey, Keith Muir, Richard Gerraty, Brian M Tress, Patricia M Desmond, for the EPITHET investigators†

3-6h

Diff/Perf avant traitement + J3-5+ Diff à 90j

CritR de Jugement principal : Croissance de l'ischémie

	Alteplase	Placebo	Difference or ratio (95% CI)*	p
Infarct growth	n=37	n=43		
Primary analytical method: geometric mean	1·24	1·78	0·69† (0·38 to 1·28)	0·239
Secondary analytical methods				
Median relative growth	1·18 (0·49 to 2·42)	1·79 (1·09 to 3·15)	0·66† (0·36 to 0·92)	0·054
Median absolute growth (mL)	4·1 (−5·29 to 57·11)	28·7 (1·01 to 64·2)	−24·6 (−40·6 to 3·2)	0·126
Mean difference in cube root volumes (cm)	0·50 (1·59)	0·75 (1·06)	−0·25 (−0·84 to 0·35)	0·415
Additional analytical methods				
Growth >0%	20 (54%)	33 (77%)	−23% (−43 to −2)	0·032
Baseline DWI lesions >5 mL				
Geometric mean growth‡	1·11	1·99	−0·56† (0·33 to 0·94)	0·028
Median relative growth‡	1·19 (0·50 to 2·36)	2·05 (1·28 to 3·25)	−0·58† (0·34 to 0·94)	0·014
Reperfusion assessed	n=34	n=43		
Reperfusion ≥90%	19 (56%)	11 (26%)	30% (9 to 51)	0·010
Median percentage reperfusion	91% (41 to 100)	65% (16 to 93)	26% (5 to 65)	0·045
Recanalisation assessed	n=19	n=28		
Recanalisation	14 (74%)	16 (57%)	17% (−10 to 44)	0·356
Clinical outcomes	n=42	n=43		
Good neurological outcome	21 (50%)	16 (37%)	13% (−8 to 34)	0·278
mRS 0–2	19 (45%)	17 (40%)	5% (−15 to 27)	0·663
mRS 0–1	15 (36%)	9 (21%)	15% (−4 to 34)	0·153

Data are mean (SD), number (%) of patients, or median (IQR). *Difference of average or percentage for alteplase minus that for placebo, unless indicated as a ratio. †Ratios. ‡Data for patients with baseline lesion >5 mL: 31 (84%) in the alteplase group and 38 (88%) in the placebo group.

Table 3: Trial outcomes for patients with mismatch

J3 ↘90% PWI

Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial

EPITHET

Lancet Neurol 2008

*Stephen M Davis, *Geoffrey A Donnan, Mark W Parsons, Christopher Levi, Kenneth S Butcher, Andre Peeters, P Alan Barber, Christopher Bladin, Deidre A De Silva, Graham Byrnes, Jonathan B Chalk, John N Fink, Thomas E Kimber, David Schultz, Peter J Hand, Judith Frayne, Graeme Hankey, Keith Muir, Richard Gerraty, Brian M Tress, Patricia M Desmond, for the EPITHET investigators†

3-6h
Diff/Perf avant traitement + J3-5+ Diff à 90j
CritR de Jugement principal : Croissance de l'ischémie

	Reperfusion	No reperfusion	Difference or ratio (95% CI)*	p
Infarct growth	n=30	n=47		
Geometric mean	0·79	2·25	0·35† (0·20 to 0·63)	0·001
Median relative growth	0·86 (0·34 to 1·75)	2·07 (1·19 to 3·65)	0·41† (0·19 to 0·81)	<0·0001
Median absolute growth (mL)	−1·0 (−9·0 to 11·2)	43·6 (4·0 to 92·3)	−44·6 (−66·7 to −12·9)	<0·0001
Mean difference in cube root volumes (cm)	−0·12 (0·77)	1·12 (1·41)	−1·24 (−1·80 to −0·67)	<0·0001
Clinical outcomes	n=30	n=47		
Good neurological outcome	22 (73%)	13 (27%)	46% (25 to 66)	<0·0001
Good functional outcome	19 (63%)	15 (32%)	31% (10 to 53)	0·007

Data are mean (SD), number (%) of patients, or median (IQR). *Difference of average or percentage for reperfusion minus that for no reperfusion, unless indicated as a ratio. †Ratios.

Table 4: Effect of reperfusion on radiological, neurological, and functional outcomes for mismatch patients

HIC symptomatiques : 7% Alteplase *vs.* 0% Placebo

EXTEND - IV

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 9, 2019 VOL. 380 NO. 19

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

H. Ma, B.C.V. Campbell, M.W. Parsons, L. Churilov, G.R. Levi, C. Hsu, T.J. Kleinig, T. Wijeratne, S. Curtze, H.M. Dewey, F. Miteff, C.-H. Tsai, J.-T. Lee, T.G. Phan, N. Mahant, M.-C. Sun, M. Krause, J. Sturm, R. Grimley, C.-H. Chen, C.-J. Hu, A.A. Wong, D. Field, Y. Sun, P.A. Barber, A. Sabet, J. Jannes, J.-S. Jeng, B. Clissold, R. Markus, C.-H. Lin, L.-M. Lien, C.F. Bladin, S. Christensen, N. Yassi, G. Sharma, A. Bivard, P.M. Desmond, B. Yan, P.J. Mitchell, V. Thijs, L. Carey, A. Meretoja, S.M. Davis, and G.A. Donnan, for the EXTEND Investigators*

- 4.5-9h
- Infarctus du réveil = Heure médiane coucher-réveil
- Diff < 70 mL - Mismatch Olig/Infarct > 1.2 et 10 mL
- Pas de TM
- CritR de Jugement principal : mRS 0-1 à 90 j

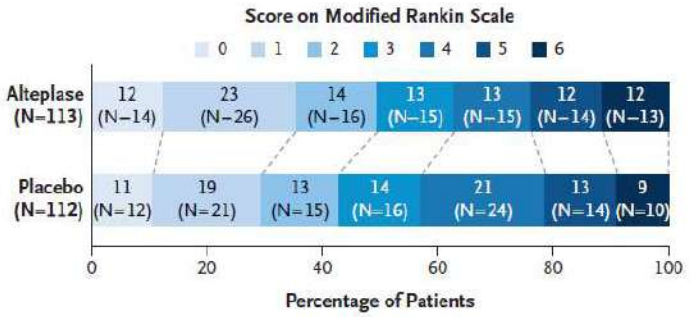


Table 2. Efficacy and Safety Outcomes.*

Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Primary outcome						
Score of 0 to 1 on the modified Rankin scale at 90 days‡	40/113 (35.4)	33/112 (29.5)	1.44 (1.01–2.06)	0.04	1.2 (0.82–1.76)	0.35
Secondary outcomes						
Score on the modified Rankin scale at 90 days						
0	14/113 (12.4)	12/112 (10.7)				
1	26/113 (23.0)	21/112 (18.8)				
2	16/113 (14.2)	15/112 (13.4)				
3	15/113 (13.3)	16/112 (14.3)				
4	15/113 (13.3)	24/112 (21.4)				
5	14/113 (12.4)	14/112 (12.5)				
6	13/113 (11.5)	10/112 (8.9)				
Functional improvement§			1.55 (0.96–2.49)		1.18 (0.74–1.87)	
Functional independence¶	56/113 (49.6)	48/112 (42.9)	1.36 (1.06–1.76)		1.16 (0.87–1.54)	
Percentage of reperfusion at 24 hr						
≥90%	53/106 (50.0)	31/109 (28.4)	1.73 (1.22–2.46)		1.76 (1.23–2.51)	
≥50%	76/106 (71.7)	57/109 (52.3)	1.35 (1.09–1.67)		1.37 (1.10–1.70)	
Tertiary outcomes						
Recanalization at 24 hr	72/107 (67.3)	43/109 (39.4%)	1.68 (1.29–2.19)		1.71 (1.30–2.23)	
Major neurologic improvement‖						
At 24 hr	27/113 (23.9)	11/112 (9.8)	2.76 (1.45–5.26)		2.43 (1.27–4.67)	
At 72 hr	32/112 (28.6)	22/112 (19.6)	1.56 (0.97–2.52)		1.45 (0.90–2.34)	
At 90 days	59/101 (58.4)	49/99 (49.5)	1.17 (0.91–1.52)		1.18 (0.91–1.53)	
Safety outcomes						
Death within 90 days after intervention	13/113 (11.5)	10/112 (8.9)	1.17 (0.57–2.40)	0.67	1.29 (0.59–2.82)	0.53
Symptomatic intracranial hemorrhage within 36 hr after intervention	7/113 (6.2)	1/112 (0.9)	7.22 (0.97–53.54)	0.053	6.94 (0.86–55.73)	0.07

EXTEND + EPITHET

JAMA Neurology | Brief Report

Association of Reperfusion After Thrombolysis With Clinical Outcome Across the 4.5- to 9-Hours and Wake-Up Stroke Time Window
A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials

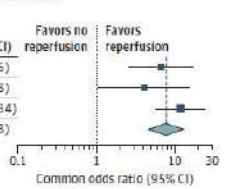
Bruce C. V. Campbell, PhD; Henry Ma, PhD; Mark W. Parsons, PhD; Leonid Churilov, PhD; Nawaf Yassi, PhD; Timothy J. Kleinig, PhD; Chung Y. Hsu, MD, PhD; Helen M. Dewey, PhD; Kenneth S. Butcher, PhD; Bernard Yan, DMedSc; Patricia M. Desmond, MD; Tissa Wijeratne, MD; Sami Curtze, MD, MSc, PhD; P. Alan Barber, PhD; Deidre A. De Silva, MBBS; Vincent Thijs, PhD; Christopher R. Levi, MBBS; Christopher F. Bladin, MD; Gagan Sharma, MCA; Andrew Bivard, PhD; Geoffrey A. Donnan, MD; Stephen M. Davis, MD

Effet de la reperfusion 4.5 - 9 h

Figure 1. Forest Plot of the Association of Reperfusion With Functional Outcome Assessed Using the Modified Rankin Scale (mRS) at 90 Days by Time to Randomization Epoch and Overall

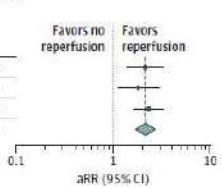
A Functional improvement in at least 1 mRS category

Stroke onset to randomization	Patients, No.	Common odds ratio (95% CI)
4.5-6 h	77	6.64 (2.62-16.86)
6-9 h	53	3.99 (1.06-15.08)
Wake-up	140	11.66 (5.59-24.34)
Overall	270	7.70 (4.64-12.78)



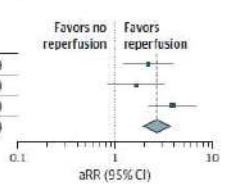
B Functional independence (mRS score of 0-2)

Stroke onset to randomization	Patients, No.	aRR (95% CI)
4.5-6 h	77	2.13 (1.39-3.25)
6-9 h	53	1.83 (1.12-2.98)
Wake-up	140	2.32 (1.64-3.28)
Overall	270	2.15 (1.71-2.72)



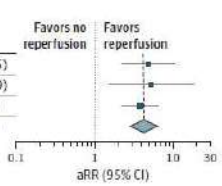
C Excellent functional outcome (mRS score of 0-1)

Stroke onset to randomization	Patients, No.	aRR (95% CI)
4.5-6 h	77	2.20 (1.25-3.88)
6-9 h	53	1.64 (0.85-3.17)
Wake-up	140	3.88 (2.25-6.70)
Overall	270	2.70 (1.93-3.78)



D Early neurological improvement

Stroke onset to randomization	Patients, No.	aRR (95% CI)
4.5-6 h	77	4.97 (2.22-11.15)
6-9 h	53	5.38 (1.53-19.00)
Wake-up	139	3.90 (2.29-6.66)
Overall	269	4.35 (2.86-6.62)



A, Functional improvement by at least 1 mRS category (ordinal analysis merging categories, 5-6). B, Functional independence (mRS score, 0-2). C, Excellent functional outcome (mRS score, 0-1). D, Early neurological improvement (8-point reduction in National Institutes of Health Stroke Scale score or reaching 0-1 at day 3). aRR indicates adjusted risk ratio.

Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data

Bruce C V Campbell, Henry Ma*, Peter A Ringleb*, Mark W Parsons, Leonid Churilov, Martin Bendszus, Christopher R Levi, Chung Hsu, Timothy J Kleinig, Marc Fatar, Didier Leys, Carlos Molina, Tissa Wijeratne, Sami Curtze, Helen M Dewey, P Alan Barber, Kenneth S Butcher, Deidre A De Silva, Christopher F Bladin, Nawaf Yassi, Johannes A R Pfaff, Gagan Sharma, Andrew Bivard, Patricia M Desmond, Stefan Schwab, Peter D Schellinger, Bernard Yan, Peter J Mitchell, Joaquín Serena, Danilo Toni, Vincent Thijs, Werner Hacke†, Stephen M Davis†, Geoffrey A Donnan†, on behalf of the EXTEND, ECASS-4, and EPITHET Investigators‡*

EXTEND + EPITHET + ECASS4

Essais avec inclusion Diff/Perf > 4.5h

	Placebo (n=201)	Alteplase (n=213)	Odds ratio* (95% CI)	p value
Primary outcome				
Excellent functional outcome (mRS score 0–1) at 3 months	58/199 (29%)	76/211 (36%)	1·86 (1·15–2·99)	0·01
Secondary outcomes				
Functional improvement in mRS score at 3 months†	NA	NA	1·60 (1·12–2·27)	0·009
Functional independence (mRS score 0–2) at 3 months	87/199 (44%)	103/211 (49%)	1·74 (1·08–2·81)	0·02
Early neurological improvement at 72 h‡	31/197 (16%)	58/206 (28%)	2·54 (1·51–4·27)	<0·0001
Safety outcomes				
Death at 3 months	18/201 (9%)	29/213 (14%)	1·55 (0·81–2·97)	0·19
Symptomatic intracerebral haemorrhage§	1/201 (<1%)	10/213 (5%)	9·70 (1·23–76·55)	0·03

Data are n/N (%). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. NA=not applicable. *Adjusted for baseline age and NIHSS. †Reduction of ≥1 point in mRS score (with mRS categories 5 and 6 merged), analysed using ordinal logistic regression. ‡Reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1 at 72 h. §Within 36h of treatment.

Table 2: Study outcomes in all patients

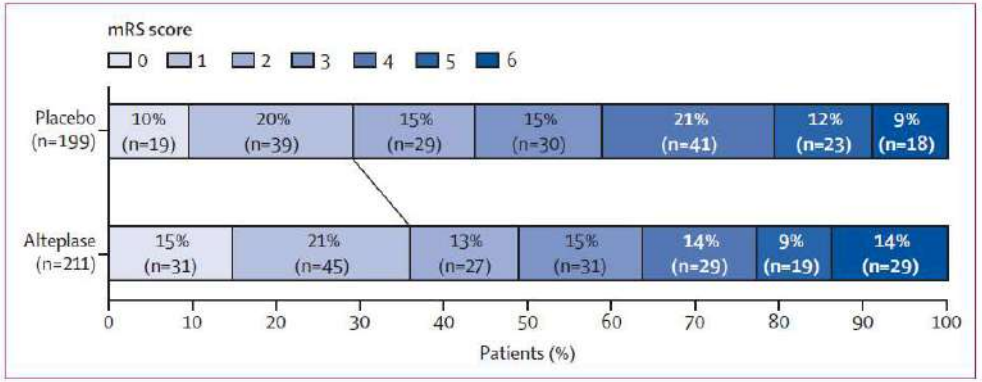


Figure 1: mRS scores at 3 months for all patients
mRS=modified Rankin Scale.

Guideline

EUROPEAN STROKE JOURNAL

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European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke

Eivind Berge[1,*], William Whiteley[2,*], Heinrich Audebert[3], Gian Marco De Marchis[4], Ana Catarina Fonseca[5], Chiara Padiglioni[6], Natalia Pérez de la Ossa[7], Daniel Strbian[8], Georgios Tsivgoulis[9,10] and Guillaume Turc[11,12,13]

Heure connue

Recommendation

For patients with ischaemic stroke of 4.5–9 h duration (known onset time) and with CT or MRI core/perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

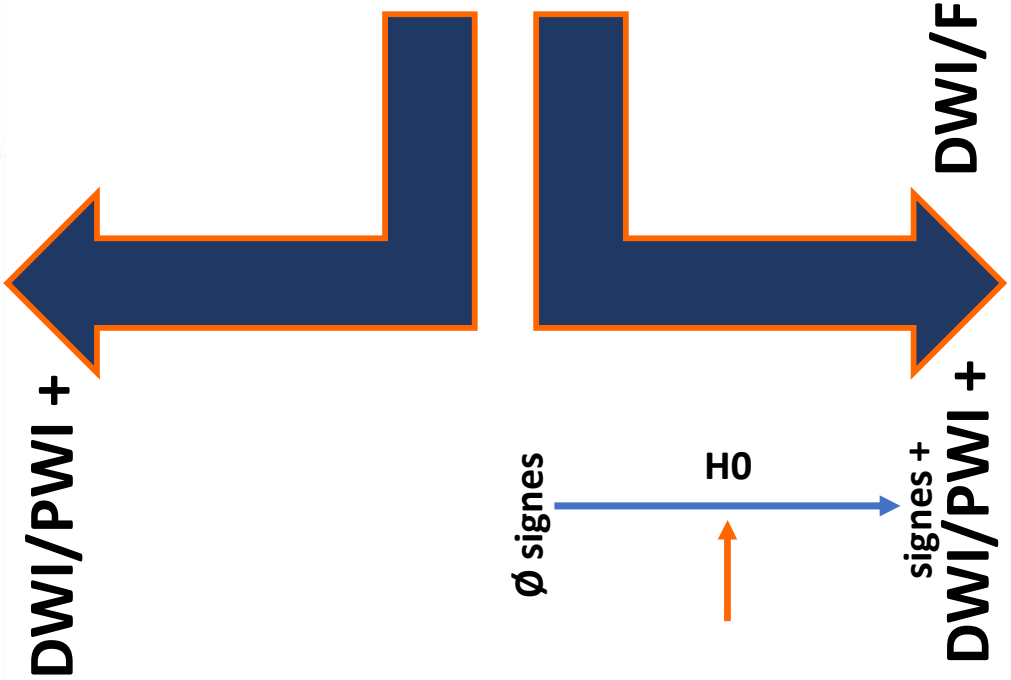
Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Strong** ↑↑

*In the individual participant data meta-analysis by Campbell et al.,[34] core/perfusion mismatch was assessed with an automated processing software and defined as follows:
- Infarct core** volume < 70 ml
- and Critically hypoperfused† volume/Infarct core** volume > 1.2
- and Mismatch volume > 10 ml

** rCBF < 30% (CT perfusion) or ADC < 620 μm²/s (Diffusion MRI)
†Tmax >6 s (perfusion CT or perfusion MRI)

For patients with no CT or MRI core/perfusion mismatch, please see the expert consensus statement below.



Heure inconnue

Recommendation

For patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.
Quality of evidence: **High** ⊕⊕⊕⊕
Strength of recommendation: **Strong** ↑↑

For patients with acute ischaemic stroke on awakening from sleep, who have CT or MRI core/perfusion mismatch* within 9 h from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.
Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Strong** ↑↑

*In the EOS individual participant data meta-analysis,[46] core/perfusion mismatch was assessed with an automated processing software and defined as follows:
- Infarct core** volume < 70 ml
- and Critically hypoperfused† volume/Infarct core** volume > 1.2
- and Mismatch volume > 10 ml

** rCBF <30% (CT perfusion) or ADC < 620 μm2/s (Diffusion MRI)
† Tmax >6 s (perfusion CT or perfusion MRI)

LES INDICATIONS DE REPERFUSION

A Connaitre les principes de la prise en charge a la phase aigüe de l'AVC ischémique TIV TM

Thrombolyse IV

Mismatch Diff/FLAIR + (WAKE-UP)

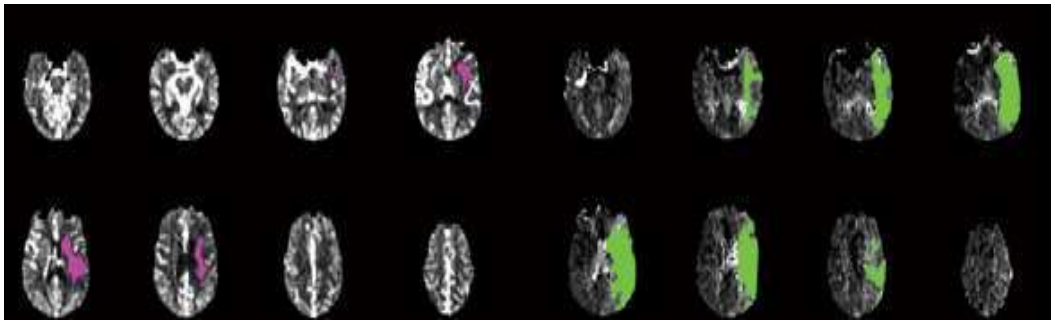
Mismatch Diff/Perf + (Extend IV)

0H **4H30** **6H** **9H** **24H**

Thrombectomie
(ACM1, CI, TB)

Mismatch Diff/Clin + (DAWN)

Mismatch Diff/Perf + (DEFUSE3)



Patients avec LVO
Dans le bras IV seule

mRS 0-2

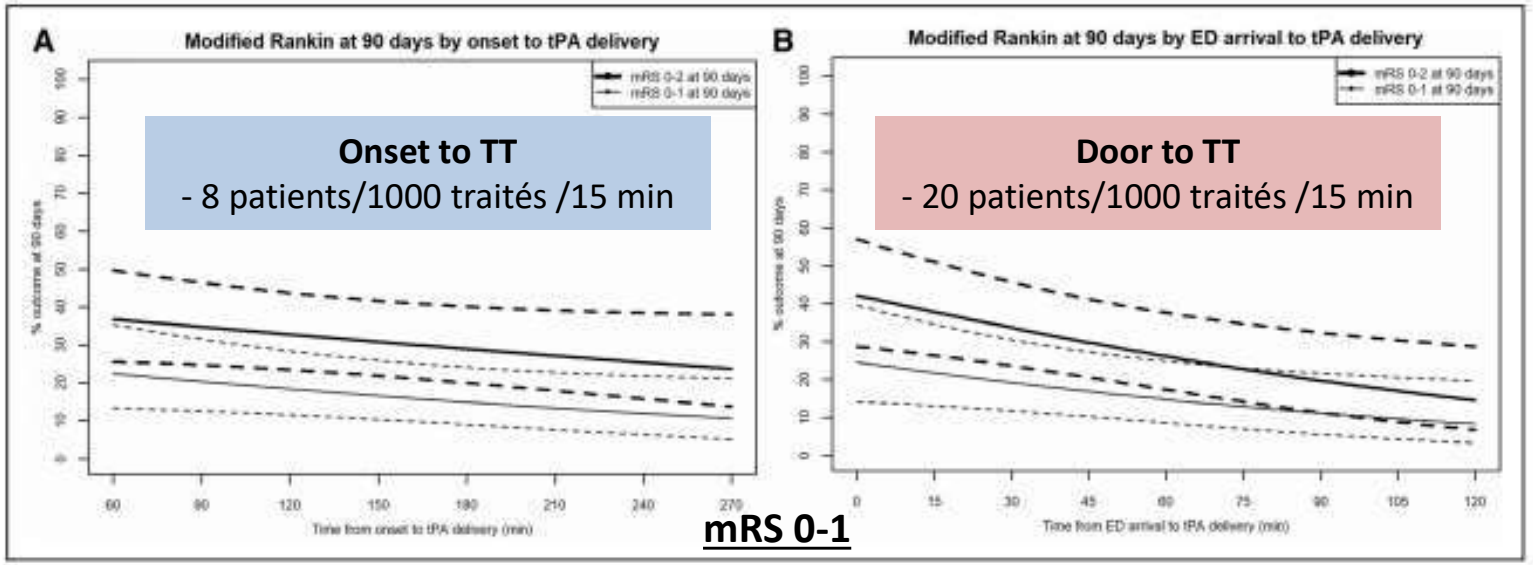
Door to TT
30-60 min vs.< 30 min
1 mRS 0-2 pour 5 patients tt

Rapid Alteplase Administration Improves Functional Outcomes in Patients With Stroke due to Large Vessel Occlusions

Meta-Analysis of the Noninterventional Arm From the HERMES Collaboration

Mayank Goyal, MD; Mohammed Almekhlafi, MD, MSc; Diederik W. Dippel, MD; Bruce C.V. Campbell, MD, PhD; Keith Muir, MD; Andrew M. Demchuk, MD; Serge Bracard, MD; Antoni Davalos, MD; Francis Guillemin, PhD; Tudor G. Jovin, MD; Bijoy K. Menon, MD, MSc; Peter J. Mitchell, MD; Scott Brown, PhD; Philip White, MD; Charles B.L.M. Majoie, MD, PhD; Jeffrey L. Saver, MD; Michael D. Hill, MD, MSc, FRCPC; for the HERMES Collaborators

Stroke 2019



Onset to TT
- 8 patients/1000 traités /15 min

Door to TT
- 20 patients/1000 traités /15 min

mRS 0-1

Figure 1. Relationship between onset-to-treatment time (**A**) and door-to-treatment time (**B**) with alteplase and the proportion of patients with 90-d functional independence (modified Rankin Scale [mRS], 0–2 in black) and 90-d excellent functional recovery (mRS, 0–1 in red). Curves are adjusted for age, sex, National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, and occlusion location. Curves have a different breadth along the time axis (abscissa), which attenuates the relative steepness of the slope of emergency department (ED)-arrival-to-tPA (tissue-type plasminogen activator)-delivery curve. A 15-min delay in start of alteplase from stroke onset was associated with 8 fewer of 1000 patients with LVO achieving excellent (mRS, 0–1) outcome at 90 d, but the loss of benefit is steeper with a 15-min delay in start of alteplase from ED arrival associated with 20 fewer of 1000 patients with LVO achieving excellent (mRS, 0–1) outcome at 90 d.

AVEC QUOI ?

Guideline

EUROPEAN STROKE JOURNAL

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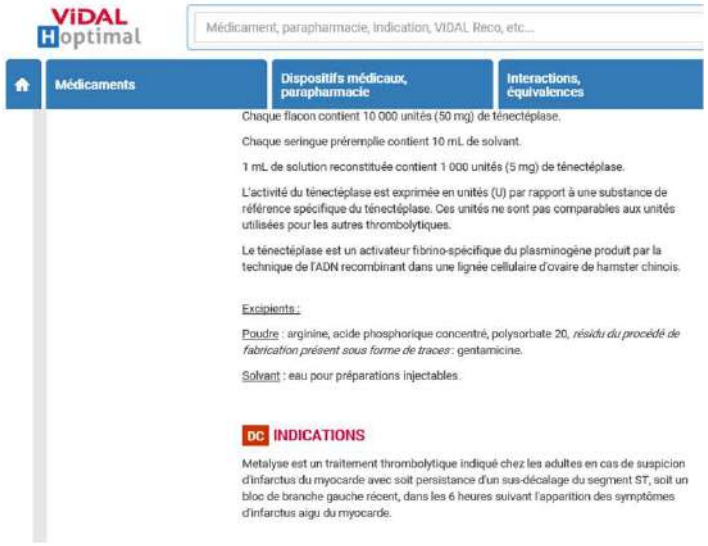
European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke

Evidence-based recommendation
For patients with acute ischaemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.
Quality of evidence: Moderate ⊕⊕⊕
Strength of recommendation: Strong ↑↑



3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	IIb	B-R	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	IIb	B-R	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.
3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.	III: No Benefit	B-R	Recommendation revised from 2013 AIS Guidelines.
Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis.[155,183–186]			See Table XLIII in online Data Supplement 1.
4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.	III: No Benefit	A	New recommendation.
Since the publication of the 2013 AIS Guidelines, 2 RCTs of sonothrombolysis as adjuvant therapy for IV thrombolysis have shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (93 patients) or sham (90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH.[187] CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) randomized 676 patients with AIS (NIHSS score ≥10) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis (335) or sham ultrasound (341).[188] Compared with the control arm, the neurological improvement, death, and serious adverse events in the intervention arm were not statistically different. At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis.			See Table XLIV in online Data Supplement 1.

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Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

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ABSTRACT

BACKGROUND

Intravenous infusion of alteplase is used for thrombolysis before endovascular thrombectomy for ischemic stroke. Tenecteplase, which is more fibrin-specific and has longer activity than alteplase, is given as a bolus and may increase the incidence of vascular reperfusion.

METHODS

We randomly assigned patients with ischemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg) within 4.5 hours after symptom onset. The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Noninferiority of tenecteplase was tested, followed by superiority. Secondary outcomes included the modified Rankin scale score (on a scale from 0 [no neurologic deficit] to 6 [death]) at 90 days. Safety outcomes were death and symptomatic intracerebral hemorrhage.

RESULTS

Of 202 patients enrolled, 101 were assigned to receive tenecteplase and 101 to receive alteplase. The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Symptomatic intracerebral hemorrhage occurred in 1% of the patients in each group.

CONCLUSIONS

Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset. (Funded by the National Health and Medical Research Council of Australia and others; EXTEND-IA TNK ClinicalTrials.gov number, NCT02388061.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Campbell at the Department of Neurology, Royal Melbourne Hospital, 300 Grattan St., Parkville, VIC 3050, Australia, or at bruce.campbell@mh.org.au.

*A list of the investigators in the EXTEND-IA TNK trial is provided in the Supplementary Appendix, available at NEJM.org.

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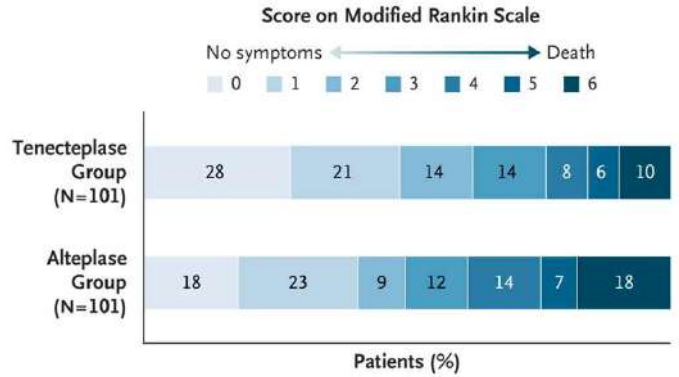
Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis†	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76



Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial *<4h30*

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Summary

Background Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.

Methods In this multicentre, open-label, parallel-group, registry-linked, randomised, controlled trial (AcT), patients were enrolled from 22 primary and comprehensive stroke centres across Canada. Patients were eligible for inclusion if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit, presenting within 4·5 h of symptom onset, and eligible for thrombolysis per Canadian guidelines. Eligible patients were randomly assigned (1:1), using a previously validated minimal sufficient balance algorithm to balance allocation by site and a secure real-time web-based server, to either intravenous tenecteplase (0·25 mg/kg to a maximum of 25 mg) or alteplase (0·9 mg/kg to a maximum of 90mg; 0·09 mg/kg as a bolus and then a 60 min infusion of the remaining 0·81 mg/kg). The primary outcome was the proportion of patients who had a modified Rankin Scale (mRS) score of 0–1 at 90–120 days after treatment, assessed via blinded review in the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment who did not withdraw consent). Non-inferiority was met if the lower 95% CI of the difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was more than −5%. Safety was assessed in all patients who received any of either thrombolytic agent and who were reported as treated. The trial is registered with ClinicalTrials.gov, NCT03889249, and is closed to accrual.

Findings Between Dec 10, 2019, and Jan 25, 2022, 1600 patients were enrolled and randomly assigned to tenecteplase (n=816) or alteplase (n=784), of whom 1577 were included in the ITT population (n=806 tenecteplase; n=771 alteplase). The median age was 74 years (IQR 63–83), 755 (47·9%) of 1577 patients were female and 822 (52·1%) were male. As of data cutoff (Jan 21, 2022), 296 (36·9%) of 802 patients in the tenecteplase group and 266 (34·8%) of 765 in the alteplase group had an mRS score of 0–1 at 90–120 days (unadjusted risk difference 2·1% [95% CI −2·6 to 6·9], meeting the prespecified non-inferiority threshold). In safety analyses, 27 (3·4%) of 800 patients in the tenecteplase group and 24 (3·2%) of 763 in the alteplase group had 24 h symptomatic intracerebral haemorrhage and 122 (15·3%) of 796 and 117 (15·4%) of 763 died within 90 days of starting treatment

Interpretation Intravenous tenecteplase (0·25 mg/kg) is a reasonable alternative to alteplase for all patients presenting with acute ischaemic stroke who meet standard criteria for thrombolysis.

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	Tenecteplase group (n=806)	Alteplase group (n=771)
Age, years	74 (63-83)	73 (62-83)
Sex		
Female	382 (47·4%)	373 (48·4%)
Male	424 (52·6%)	398 (51·6%)
Baseline NIHSS score (n=1569)	9 (6-16)	10 (6-17)
Baseline NIHSS score categories		
<8	325/803 (40·5%)	294/766 (38·4%)
8–15	247/803 (30·8%)	256/766 (33·4%)
>15	231/803 (28·8%)	216/766 (28·2%)
Occlusion site on baseline CT angiography (n=1558)*		
Intracranial internal carotid artery	69/801 (8·6%)	66/757 (8·7%)
M1 segment MCA	118/801 (14·7%)	119/757 (15·7%)
M2 segment MCA	174/801 (21·7%)	141/757 (18·6%)
Other distal occlusions†	130/801 (16·2%)	138/757 (18·2%)
Vertebrobasilar arterial system	26/801 (3·2%)	38/757 (5·0%)
Cervical internal carotid artery	17/801 (2·1%)	9/757 (1·2%)
No visible occlusions	267/801 (33·3%)	246/757 (32·5%)
Presence of large vessel occlusion on baseline CT angiography (n=1558)	196/801 (24·5%)	193/757 (25·5%)
Type of enrolling centre		
Primary stroke centre	56/806 (6·9%)	43/771 (5·6%)
Comprehensive stroke centre	750/806 (93·1%)	728/771 (94·4%)
Source registry		
QuiCR	346/806 (42·9%)	342/771 (44·4%)
OPTIMISE	460/806 (57·1%)	429/771 (55·6%)
Workflow times, min		
Stroke symptom onset to hospital arrival (n=1560)	82 (54-140)	83 (55-138)
Stroke symptom onset to randomisation (n=1570)	121 (85-179)	123 (88-179)
Door (hospital arrival) to baseline CT (n=1561)	15 (12-21)	16 (12-22)
Stroke symptom onset to needle (intravenous thrombolysis start; n=1562)	128 (93-186)	131 (95-188)
Door (hospital arrival) to needle (intravenous thrombolysis start; n=1556)	36 (27-49)	37 (29-52)
Baseline CT to arterial puncture (in patients undergoing EVT; n=505)	60 (43-88)	58 (41-85)
Arterial puncture to successful reperfusion (in patients undergoing EVT; n=445)	31 (19-47)	27 (17-45)

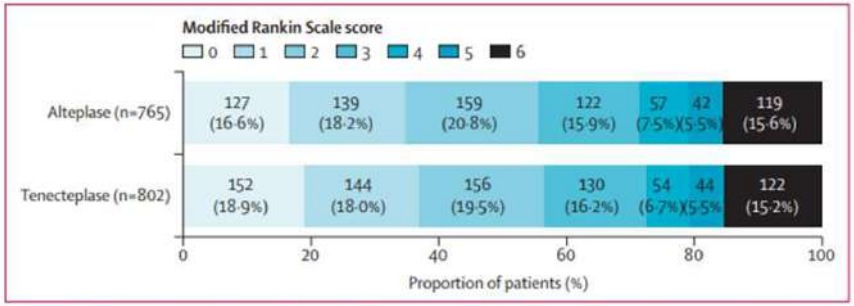

Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat population**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Review

Non inferiority

Thrombolysis for acute ischaemic stroke: current status and future perspectives

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Alteplase is currently the only approved thrombolytic agent for treatment of acute ischaemic stroke, but interest is burgeoning in the development of new thrombolytic agents for systemic reperfusion with an improved safety profile, increased efficacy, and convenient delivery. Tenecteplase has emerged as a potential alternative thrombolytic agent that might be preferred over alteplase because of its ease of administration and reported efficacy in patients with large vessel occlusion. Ongoing research efforts are also looking at potential improvements in recanalisation with the use of adjunct therapies to intravenous thrombolysis. New treatment strategies are also emerging that aim to reduce the risk of vessel reocclusion after intravenous thrombolysis administration. Other research endeavors are looking at the use of intra-arterial thrombolysis after mechanical thrombectomy to induce tissue reperfusion. The growing implementation of mobile stroke units and advanced neuroimaging could boost the number of patients who can receive intravenous thrombolysis by shortening onset-to-treatment times and identifying patients with salvageable penumbra. Continued improvements in this area will be essential to facilitate the ongoing research endeavors and to improve delivery of new interventions.

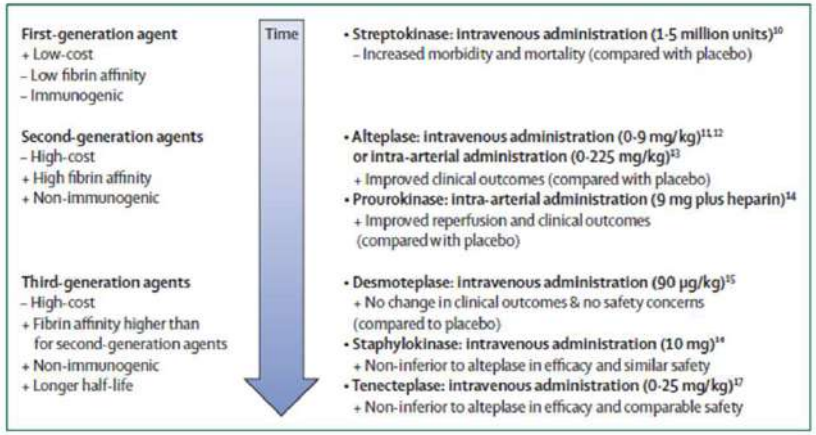

Figure 1: **Thrombolytic agents for the treatment of acute ischaemic stroke**
Repeat exposure to immunogenic agents can cause severe allergic reactions, including anaphylaxis. Schematic overview of the results of major trials of thrombolytic agents, from early first-generation agents to current third-generation drugs. High fibrin affinity translates into greater potency for thrombolysis, at the same time preserving the integrity of systemic coagulation. +=advantage of the agent. –=disadvantage of the agent.

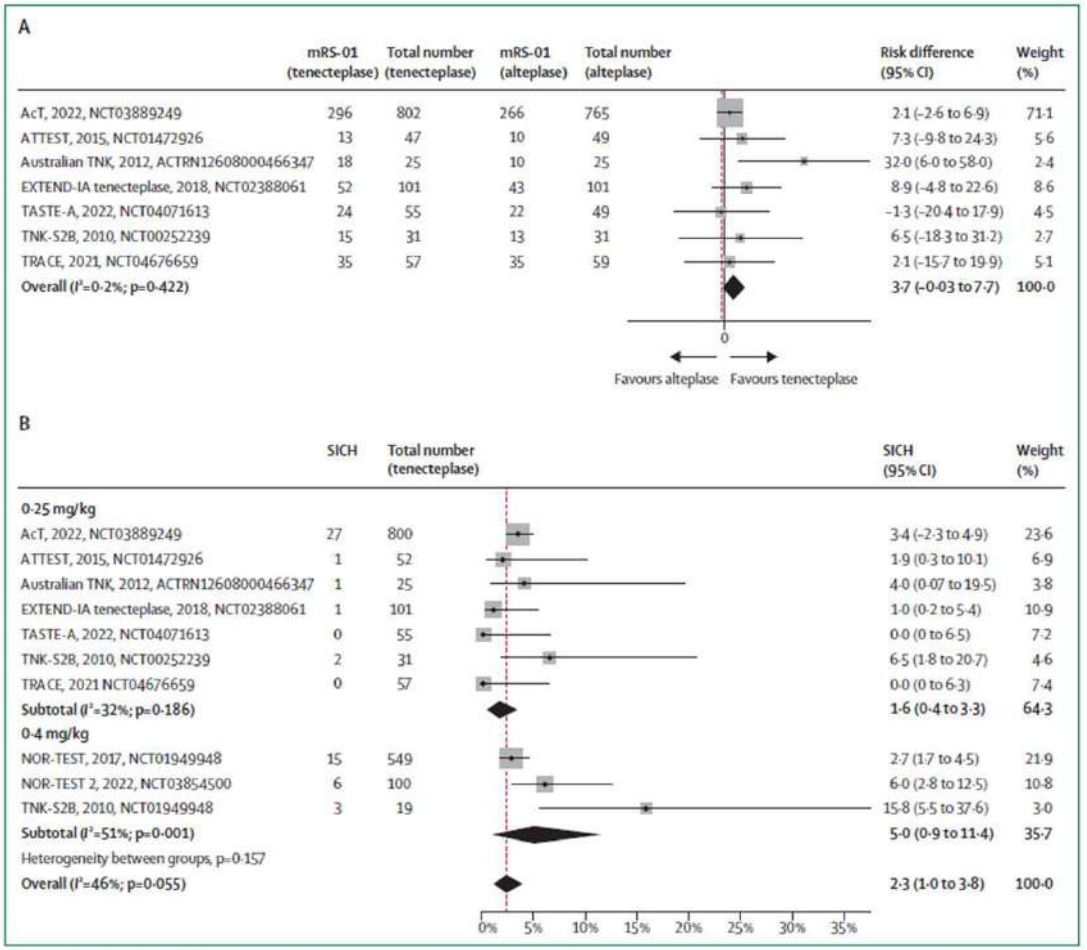

Figure 3: **Pooled analyses of data from randomised trials of intravenous thrombolysis for acute ischaemic stroke, comparing tenecteplase with alteplase**
(A) Forest plot shows risk differences in excellent functional outcome (modified Rankin scale scores of 0–1) or return to baseline disability status at 3 months for patients receiving either tenecteplase 0·25 mg/kg or alteplase 0·9 mg/kg. Red dashed line corresponds to a non-inferiority margin of –1·3%. (B) Forest plot shows crude proportions of symptomatic intracranial haemorrhage in patients treated with either 0·25 mg/kg or 0·40 mg/kg of intravenous tenecteplase. Red dashed line corresponds to the pooled estimate of 2·3%. Further information on the statistical analyses for these forest plots is provided in the appendix (p 3). SICH=symptomatic intracranial haemorrhage.

LVO – Superiority TICI + mRS

Stroke

BRIEF REPORT

Intravenous Thrombolysis With Tenecteplase in Patients With Large Vessel Occlusions

Systematic Review and Meta-Analysis

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BACKGROUND AND PURPOSE: Accumulating evidence from randomized controlled clinical trials suggests that tenecteplase may represent an effective treatment alternative to alteplase for acute ischemic stroke. In the present systematic review and meta-analysis, we sought to compare the efficacy and safety outcomes of intravenous tenecteplase to intravenous alteplase administration for acute ischemic stroke patients with large vessel occlusions (LVOs).

METHODS: We searched MEDLINE (Medical Literature Analysis and Retrieval System Online) and Scopus for published randomized controlled clinical trials providing outcomes of acute ischemic stroke with confirmed LVO receiving intravenous thrombolysis with either tenecteplase at different doses or alteplase at a standard dose of 0.9 mg/kg. The primary outcome was the odds of modified Rankin Scale score of 0 to 2 at 3 months.

RESULTS: We included 4 randomized controlled clinical trials including a total of 433 patients. Patients with confirmed LVO receiving tenecteplase had higher odds of modified Rankin Scale scores of 0 to 2 (odds ratio, 2.06 [95% CI, 1.15–3.69]), successful recanalization (odds ratio, 3.05 [95% CI, 1.73–5.40]), and functional improvement defined as 1-point decrease across all modified Rankin Scale grades (common odds ratio, 1.84 [95% CI, 1.18–2.87]) at 3 months compared with patients with confirmed LVO receiving alteplase. There was little or no heterogeneity between the results provided from included studies regarding the aforementioned outcomes ($I^2 \leq 20\%$). No difference in the outcomes of early neurological improvement, symptomatic intracranial hemorrhage, any intracranial hemorrhage, and the rates of modified Rankin Scale score 0 to 1 or all-cause mortality at 3 months was detected between patients with LVO receiving intravenous thrombolysis with either tenecteplase or alteplase.

CONCLUSIONS: Acute ischemic stroke patients with LVO receiving intravenous thrombolysis with tenecteplase have significantly better recanalization and clinical outcomes compared with patients receiving intravenous alteplase.

Key Words: brain ischemia ■ humans ■ odds ratio ■ reperfusion ■ tenecteplase

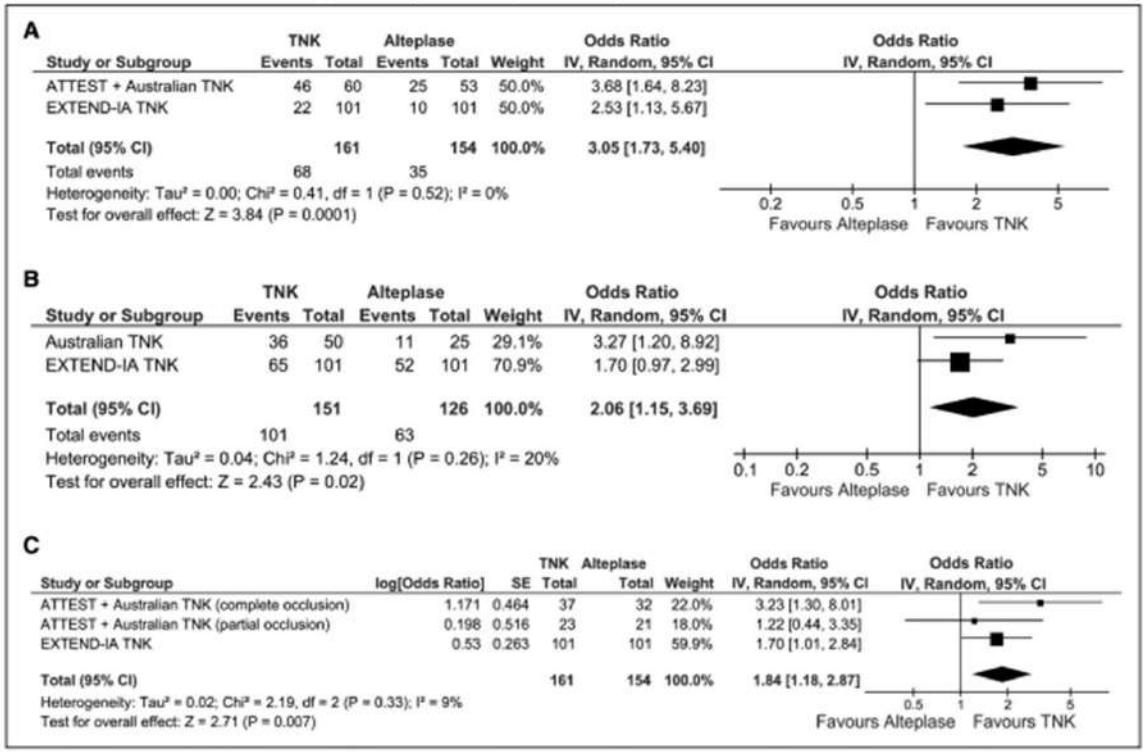

Figure. Outcomes of patients with acute large vessel occlusions receiving intravenous tenecteplase compared to intravenous alteplase.

Forest plots on the odds of (**A**) successful recanalization, (**B**) modified Rankin Scale score of 0 to 2 at 3 mo, and (**C**) functional improvement at 3 mo between patients with acute large vessel occlusions randomized to intravenous tenecteplase or alteplase. ATTEST indicates Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; EXTEND-IA, Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; IV, inverse variance; and TNK, tenecteplase.

Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial <4h30

*Andrew Bivard, Henry Zhao, Leonid Churilov, Bruce C V Campbell, Skye Coote, Nawaf Yassi, Bernard Yan, Michael Valente, Angelos Sharobeam, Anna H Balabanski, Angela Dos Santos, Jo Lyn Ng, Vignan Yogendrakumar, Felix Ng, Francesca Langenberg, Damien Easton, Alex Warwick, Elizabeth Mackey, Amy MacDonald BN, Gagan Sharma, Michael Stephenson, Karen Smith, David Anderson, Philip Choi, Vincent Thijs, Henry Ma, Geoffrey C Cloud, Tissa Wijeratne, Liudmyla Olenko, Dominic Italiano, Stephen M Davis, Geoffrey A Donnan, Mark W Parsons, on behalf of the TASTE-A collaborators**

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See Comment page 496

**TASTE-A collaborators listed at the end of the Article

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Summary

Background Mobile stroke units (MSUs) equipped with a CT scanner reduce time to thrombolytic treatment and improve patient outcomes. We tested the hypothesis that tenecteplase administered in an MSU would result in superior reperfusion at hospital arrival, when compared with alteplase.

Methods The TASTE-A trial is a phase 2, randomised, open-label trial at the Melbourne MSU and five tertiary hospitals in Melbourne, VIC, Australia. Patients (aged ≥18 years) with ischaemic stroke who were eligible for thrombolytic treatment were randomly allocated in the MSU to receive, within 4·5 h of symptom onset, either standard-of-care alteplase (0·9 mg/kg [maximum 90 mg], administered intravenously with 10% as a bolus over 1 min and 90% as an infusion over 1 h), or the investigational product tenecteplase (0·25 mg/kg [maximum 25 mg], administered as an intravenous bolus over 10 s), before being transported to hospital for ongoing care. The primary outcome was the volume of the perfusion lesion on arrival at hospital, assessed by CT-perfusion imaging. Secondary safety outcomes were modified Rankin Scale (mRS) score of 5 or 6 at 90 days, symptomatic intracerebral haemorrhage and any haemorrhage within 36 h, and death at 90 days. Assessors were masked to treatment allocation. Analysis was by intention-to-treat. The trial was registered with ClinicalTrials.gov, NCT04071613, and is completed.

Findings Between June 20, 2019, and Nov 16, 2021, 104 patients were enrolled and randomly allocated to receive either tenecteplase (n=55) or alteplase (n=49). The median age of patients was 73 years (IQR 61–83), and the median NIHSS at baseline was 8 (5–14). On arrival at the hospital, the perfusion lesion volume was significantly smaller with tenecteplase (median 12 mL [IQR 3–28]) than with alteplase (35 mL [18–76]; adjusted incidence rate ratio 0·55, 95% CI 0·37–0·81; p=0·0030). At 90 days, an mRS of 5 or 6 was reported in eight (15%) patients allocated to tenecteplase and ten (20%) patients allocated to alteplase (adjusted odds ratio [aOR] 0·70, 95% CI 0·23–2·16; p=0·54). Five (9%) patients allocated to tenecteplase and five (10%) patients allocated to alteplase died from any cause at 90 days (aOR 1·12, 95% CI 0·26–4·90; p=0·88). No cases of symptomatic intracerebral haemorrhage were reported within 36 h with either treatment. Up to day 90, 13 serious adverse events were noted: five (5%) in patients treated with tenecteplase, and eight (8%) in patients treated with alteplase.

Interpretation Treatment with tenecteplase on the MSU in Melbourne resulted in a superior rate of early reperfusion compared with alteplase, and no safety concerns were noted. This trial provides evidence to support the use of tenecteplase and MSUs in an optimal model of stroke care.

Funding Melbourne Academic Centre for Health.

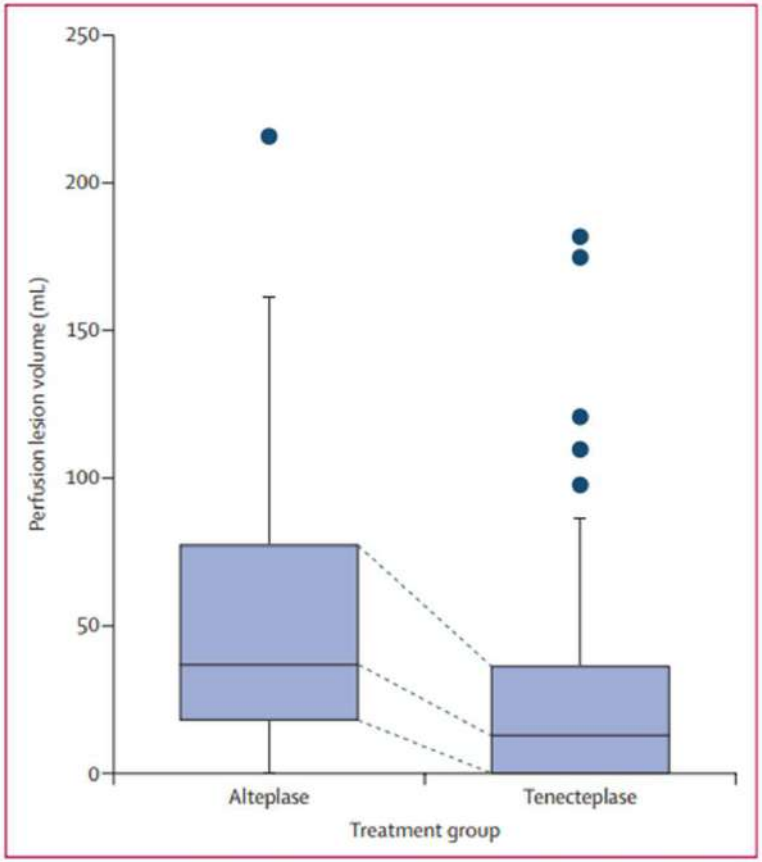

Figure 2: **Perfusion lesion volume on CT perfusion imaging performed on arrival at the receiving hospital by treatment group**

Horizontal lines represent the 25th percentile, median, and 75 percentile. The whiskers extend up to 1·5 times the IQR range distance from the 75th and 25th percentiles, but no further than the minimum or maximum. Individual dots represent the values beyond the range of the whiskers.

For any TIV

Guideline

EUROPEAN STROKE JOURNAL

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European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke

Sonia Alamowitch[1], Guillaume Turc[2,3,4,5], Lina Palaiodimou[6], Andrew Bivard[7], Alan Cameron[8], Gian Marco De Marchis[9,10], Annette Fromm[11], Janika Kõrv[12], Melinda B Roaldsen[13], Aristeidis H Katsanos[14] and Georgios Tsivgoulis[6*]

Evidence-based recommendation
For patients with acute ischaemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.
Quality of evidence: Moderate ⊕⊕⊕
Strength of recommendation: Strong ↑↑

Expert consensus statement
All MWG members suggest favouring tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg for patients with acute ischaemic stroke of <4.5 hrs duration in light of safety and efficacy data and because tenecteplase can be administered with a single bolus rather than a 1-hr infusion.
Voting: 9/9 members

Table 1. GRADE evidence profile for PICO 1.1.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNK (0.25 mg/kg)	Alteplase (0.9 mg/kg)	Relative (95% CI)	Absolute (95% CI)		
Excellent functional outcome (modified Rankin Scale scores 0–1) at 90 days												
7	Randomised trials	Serious[a,b]	Not serious	Not serious	Not serious	None	449/1118 (40.2%)	395/1079 (36.6%)	OR 1.17 (0.98 to 1.39)	37 more per 1000 (from 5 fewer to 79 more)	⊕⊕⊕◯ Moderate	CRITICAL
Good functional outcome (modified Rankin Scale scores 0–2) at 90 days												
6	Randomised trials	Serious[b]	Serious[c]	Not serious	Not serious	None	632/1087 (58.1%)	575/1047 (54.9%)	OR 1.36 (0.92 to 2.00)	74 more per 1000 (from 21 fewer to 160 more)	⊕⊕◯◯ Low	CRITICAL
Reduced disability (1 point or more reduction across all modified Rankin Scale scores) at 90 days												
5	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	1062 (N/A)	1022 (N/A)	cOR 1.13 (0.97 to 1.31)	N/A	⊕⊕⊕◯ Moderate	CRITICAL
Symptomatic intracranial haemorrhage (sICH) at 24–48 h												
7	Randomised trials	Serious[a,b]	Not serious	Serious[d]	Not serious	None	32/1121 (2.9%)	32/1079 (3.0%)	OR 0.98 (0.59 to 1.62)	1 fewer per 1000 (from 12 fewer to 18 more)	⊕⊕◯◯ Low	CRITICAL
Mortality at 90 days												
7	Randomised trials	Serious[a,b]	Not serious	Not serious	Not serious	None	154/1112 (13.8%)	163/1077 (15.1%)	OR 0.88 (0.65 to 1.19)	17 fewer per 1,000 (from 49 fewer to 24 more)	⊕⊕⊕◯ Moderate	CRITICAL
Major neurological improvement (according to definitions used in individual trials) at 24–72 h												
4	randomised trials	very serious[a,b]	serious[c]	serious[d]	serious[f]	none	123/204 (60.3%)	95/206 (46.1%)	OR 2.44 (1.09 to 5.46)	215 more per 1,000 (from 21 more to 363 more)	⊕◯◯◯ Very low	IMPORTANT
Any intracranial haemorrhage (ICH)												
7	Randomised trials	Serious[a,b]	Not serious	Serious[d]	Not serious	None	176/1121 (15.7%)	189/879 (21.5%)	OR 0.62 (0.49 to 0.79)	73 fewer per 1000 (from 101 fewer to 41 fewer)	⊕⊕◯◯ Low	IMPORTANT
Extracranial bleeding												
5	Randomised trials	Serious[a,b]	Not serious	Serious[d]	Not serious	None	32/1041 (3.1%)	25/1005 (2.5%)	OR 1.23 (0.60 to 2.53)	6 more per 1000 (from 10 fewer to 36 more)	⊕⊕◯◯ Low	IMPORTANT
Final infarct volume at 24 h (cm^3)												
2	Randomised trials	Very serious[b,e]	Not serious	Serious[d]	Not serious	None	78	66	N/A	4.5 cm^3 more (3.1 less to 12.2 more)*	⊕◯◯◯ Very low	IMPORTANT
Ischaemic core growth within 24 h (cm^3)												
2	Randomised trials	Very serious[e]	Not serious	Not serious	Serious[f]	None	56	42	N/A	2.1 cm^3 less (4.4 less to 0.3 more)**	⊕◯◯◯ Very low	IMPORTANT
Door-to-needle time (min)												
2	Randomised trials	Very serious[e]	Serious[c]	Not serious	Serious[f]	None	856	805	N/A	3.7 min less (9.5 less to 2.2 more)**	⊕◯◯◯ Very low	IMPORTANT
Onset-to-treatment time (min)												
4	Randomised trials	Serious[b]	Not serious	Not serious	Serious[f]	None	1087	1048	N/A	5.2 min less (12.1 less to 1.7 more)**	⊕⊕◯◯ Low	IMPORTANT

For LVO

Guideline

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Evidence-based recommendation

For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis, we recommend tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg. Intravenous thrombolysis should not delay mechanical thrombectomy.
Quality of evidence: Moderate ⊕⊕⊕
Strength of recommendation: Strong ↑↑

Expert consensus statement

For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are directly admitted to a thrombectomy-capable center, all MWG members suggest IVT with tenecteplase 0.25 mg/kg or 0.40 mg/kg over skipping IVT.
For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are admitted to a center without mechanical thrombectomy capability, all MWG members suggest IVT with tenecteplase 0.25 mg/kg followed by rapid transfer to a thrombectomy-capable center.
Voting: 9/9 members

Table 4. GRADE evidence profile for PICO 2.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNK (0.25 mg/kg)	alteplase (0.9mg/kg)	Relative (95% CI)	Absolute (95% CI)		
Good functional outcome (modified Rankin Scale scores 0–2) at 90 days												
3	Randomised trials	Not serious	Serious[a]	Not serious	Not serious	None	148/322 (46.0%)	111/319 (34.8%)	OR 1.91 (1.05 to 3.48)	157 more per 1000 (from 11 more to 302 more)	⊕⊕◯◯ Moderate	CRITICAL
Excellent functional outcome (modified Rankin Scale scores 0–1) at 90 days												
4	Randomised trials	Very serious[b,c]	Not serious	Not serious	Not serious	None	99/334 (30.5%)	68/326 (21.3%)	OR 1.69 (1.15 to 2.47)	100 more per 1000 (from 24 more to 186 more)	⊕⊕◯◯ Low	CRITICAL
Reduced disability (1 point or more reduction across all modified Rankin Scale scores) at 90 days												
4	Randomised trials	Very serious[b,c]	Serious[a]	Not serious	Not serious	None	357 (N/A)	347 (N/A)	cOR 1.63 (1.05 to 2.54)	N/A	⊕◯◯◯ Very low	CRITICAL
Mortality at 90 days												
3	Randomised trials	Serious[c]	Not serious	Not serious	Not serious	None	49/322 (15.2%)	62/319 (19.4%)	OR 0.75 (0.49 to 1.13)	41 fewer per 1000 (from 89 fewer to 20 more)	⊕⊕⊕◯ Moderate	CRITICAL
Symptomatic intracranial haemorrhage (sICH) at 24–48 h												
2	Randomised trials	Serious[d]	Not serious	Not serious	Serious[e]	None	2/126 (1.6%)	4/126 (3.2%)	OR 0.50 (0.08 to 2.99)	16 fewer per 1000 (from 29 fewer to 58 more)	⊕⊕◯◯ Low	CRITICAL
Recanalisation before endovascular thrombectomy (EVT) at first angiographic acquisition or averted EVT												
2	Randomised trials	None	Serious[a]	Not serious	Serious[e]	None	48/357 (13.4%)	37/357 (10.4%)	OR 1.49 (0.58 to 3.85)	43 more per 1000 (from 41 fewer to 204 more)	⊕⊕◯◯ Low	CRITICAL
Recanalisation within 24 h												
3	Randomised trials	Very serious[b,c,d]	Not serious	Serious[f]	Serious[e]	None	109/134 (81.3%)	93/131 (71.0%)	OR 2.07 (0.87 to 4.96)	125 more per 1000 (from 29 fewer to 214 [illegible]	⊕◯◯◯ Very low	CRITICAL
Onset-to-treatment time (min)												
2	Randomised trials	Serious[d]	Serious[a]	Not serious	Serious[e]	None	126	126	N/A	1.8 min more (2.57 less to 29.2 more)[g]	⊕◯◯◯ Very low	IMPORTANT
Major neurological improvement (according to definitions used in individual trials) at 24–72 h												
2	Randomised trials	Serious[d]	Serious[a]	Serious[f]	Serious[e]	None	93/126 (73.8%)	78/126 (61.9%)	OR 3.00 (0.39 to 23.11)	211 more per 1000 (from 231 fewer to 355 more)	⊕⊕◯◯ Low	IMPORTANT
Any intracranial haemorrhage (ICH)												
2	Randomised trials	Serious[d]	Serious[a]	Not serious	Serious[e]	None	7/126 (5.6%)	10/126 (7.9%)	OR 0.56 (0.09 to 3.75)	33 fewer per 1000 (from 73 fewer to 168 more)	⊕◯◯◯ Very low	IMPORTANT

ORIGINAL ARTICLE

Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy *Despite LVO*

Authors: Yunyun Xiong, M.D., Ph.D., Bruce C.V. Campbell, M.B., B.S., Ph.D., Lee H. Schwamm, M.D., Xia Meng, M.D., Ph.D., Aoming Jin, Ph.D., Mark W. Parsons, M.B., B.S., Ph.D., Marc Fisher, M.D., +23, for the TRACE-III Investigators* Author Info & Affiliations

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CME

Abstract

BACKGROUND

Tenecteplase is an effective thrombolytic agent for eligible patients with stroke who are treated within 4.5 hours after the onset of stroke. However, data regarding the effectiveness of tenecteplase beyond 4.5 hours are limited.

METHODS

In a trial conducted in China, we randomly assigned patients with large-vessel occlusion of the middle cerebral artery or internal carotid artery who had salvageable brain tissue as identified on perfusion imaging and who did not have access to endovascular thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or standard medical treatment 4.5 to 24 hours after the time that the patient was last known to be well (including after stroke on awakening and unwitnessed stroke). The primary outcome was the absence of disability, which was defined as a score of 0 or 1 on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability), at day 90. The key safety outcomes were symptomatic intracranial hemorrhage and death.

RESULTS

A total of 516 patients were enrolled; 264 were randomly assigned to receive tenecteplase and 252 to receive standard medical treatment. Less than 2% of the patients (4 in the tenecteplase group and 5 in the standard-treatment group) underwent rescue endovascular thrombectomy. Treatment with tenecteplase resulted in a higher percentage of patients with a modified Rankin scale score of 0 or 1 at 90 days than standard medical treatment (33.0% vs. 24.2%; relative rate, 1.37; 95% confidence interval, 1.04 to 1.81; P=0.03). Mortality at 90 days was 13.3% with tenecteplase and 13.1% with standard medical treatment, and the incidence of symptomatic intracranial hemorrhage within 36 hours after treatment was 3.0% and 0.8%, respectively.

Download a PDF of the Plain Language Summary.

CONCLUSIONS

In this trial involving Chinese patients with ischemic stroke due to large-vessel occlusion, most of whom did not undergo endovascular thrombectomy, treatment with tenecteplase administered 4.5 to 24 hours after stroke onset resulted in less disability and similar survival as compared with standard medical treatment, and the incidence of symptomatic intracranial hemorrhage appeared to be higher. (Funded by the National Natural Science Foundation of China and others; TRACE-III ClinicalTrials.gov number, NCT05141305.)

MAIS…

Guideline

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European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke

Sonia Alamowitch[1], Guillaume Turc[2,3,4,5], Lina Palaiodimou[6], Andrew Bivard[7], Alan Cameron[8], Gian Marco De Marchis[9,10], Annette Fromm[11], Janika Kõrv[12], Melinda B Roaldsen[13], Aristeidis H Katsanos[14] and Georgios Tsivgoulis[6*]

Evidence-based recommendation
For patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis, there is continued uncertainty over the potential benefits and harms of tenecteplase compared with alteplase.
Quality of evidence: Very low ⊕
Strength of recommendation: -

Expert consensus statement
All MWG members suggest that tenecteplase 0.25 mg/kg could be a reasonable alternative to alteplase 0.9 mg/kg for patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis after selection with advanced imaging (FLAIR-DWI mismatch or perfusion mismatch as outlined in the 2021 ESO Guidelines on IVT).
Voting: 9/9 members

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection

G.W. Albers, M. Jumaa, B. Purdon, S.F. Zaidi, C. Streib, A. Shuaib, N. Sangha, M. Kim, M.T. Froehler, N.E. Schwartz, W.M. Clark, C.E. Kircher, M. Yang, L. Massaro, X.-Y. Lu, G.A. Rippon, J.P. Broderick, K. Butcher, M.G. Lansberg, D.S. Liebeskind, A. Nouh, L.H. Schwamm, and B.C.V. Campbell, for the TIMELESS Investigators*

ABSTRACT

BACKGROUND
Thrombolytic agents, including tenecteplase, are generally used within 4.5 hours after the onset of stroke symptoms. Information on whether tenecteplase confers benefit beyond 4.5 hours is limited.

METHODS
We conducted a multicenter, double-blind, randomized, placebo-controlled trial involving patients with ischemic stroke to compare tenecteplase (0.25 mg per kilogram of body weight, up to 25 mg) with placebo administered 4.5 to 24 hours after the time that the patient was last known to be well. Patients had to have evidence of occlusion of the middle cerebral artery or internal carotid artery and salvageable tissue as determined on perfusion imaging. The primary outcome was the ordinal score on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability and a score of 6 indicating death) at day 90. Safety outcomes included death and symptomatic intracranial hemorrhage.

RESULTS
The trial enrolled 458 patients, 77.3% of whom subsequently underwent thrombectomy; 228 patients were assigned to receive tenecteplase, and 230 to receive placebo. The median time between the time the patient was last known to be well and randomization was approximately 12 hours in the tenecteplase group and approximately 13 hours in the placebo group. The median score on the modified Rankin scale at 90 days was 3 in each group. The adjusted common odds ratio for the distribution of scores on the modified Rankin scale at 90 days for tenecteplase as compared with placebo was 1.13 (95% confidence interval, 0.82 to 1.57; P=0.45). In the safety population, mortality at 90 days was 19.7% in the tenecteplase group and 18.2% in the placebo group, and the incidence of symptomatic intracranial hemorrhage was 3.2% and 2.3%, respectively.

CONCLUSIONS
Tenecteplase therapy that was initiated 4.5 to 24 hours after stroke onset in patients with occlusions of the middle cerebral artery or internal carotid artery, most of whom had undergone endovascular thrombectomy, did not result in better clinical outcomes than those with placebo. The incidence of symptomatic intracerebral hemorrhage was similar in the two groups. (Funded by Genentech; TIMELESS ClinicalTrials.gov number, NCT03785678.)

Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial

Summary
Background Individuals with minor ischaemic stroke and intracranial occlusion are at increased risk of poor outcomes. Intravenous thrombolysis with tenecteplase might improve outcomes in this population. We aimed to test the superiority of intravenous tenecteplase over non-thrombolytic standard of care in patients with minor ischaemic stroke and intracranial occlusion or focal perfusion abnormality.

Methods In this multicentre, prospective, parallel group, open label with blinded outcome assessment, randomised controlled trial, adult patients (aged ≥18 years) were included at 48 hospitals in Australia, Austria, Brazil, Canada, Finland, Ireland, New Zealand, Singapore, Spain, and the UK. Eligible patients with minor acute ischaemic stroke (National Institutes of Health Stroke Scale score 0–5) and intracranial occlusion or focal perfusion abnormality were enrolled within 12 h from stroke onset. Participants were randomly assigned (1:1), using a minimal sufficient balance algorithm to intravenous tenecteplase (0·25 mg/kg) or non-thrombolytic standard of care (control). Primary outcome was a return to baseline functioning on pre-morbid modified Rankin Scale score in the intention-to-treat (ITT) population (all patients randomly assigned to a treatment group and who did not withdraw consent to participate) assessed at 90 days. Safety outcomes were reported in the ITT population and included symptomatic intracranial haemorrhage and death. This trial is registered with ClinicalTrials.gov, NCT02398656, and is closed to accrual.

Findings The trial was stopped early for futility. Between April 27, 2015, and Jan 19, 2024, 886 patients were enrolled; 369 (42%) were female and 517 (58%) were male. 454 (51%) were assigned to control and 432 (49%) to intravenous tenecteplase. The primary outcome occurred in 338 (75%) of 452 patients in the control group and 309 (72%) of 432 in the tenecteplase group (risk ratio [RR] 0·96, 95% CI 0·88–1·04, p=0·29). More patients died in the tenecteplase group (20 deaths [5%]) than in the control group (five deaths [1%]; adjusted hazard ratio 3·8; 95% CI 1·4–10·2, p=0·0085). There were eight (2%) symptomatic intracranial haemorrhages in the tenecteplase group versus two (<1%) in the control group (RR 4·2; 95% CI 0·9–19·7, p=0·059).

Interpretation There was no benefit and possible harm from treatment with intravenous tenecteplase. Patients with minor stroke and intracranial occlusion should not be routinely treated with intravenous thrombolysis.

Funding Heart and Stroke Foundation of Canada, Canadian Institutes of Health Research, and the British Heart Foundation.

Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial

Summary
Background Current evidence supports the use of intravenous thrombolysis with alteplase in patients with wake-up stroke selected with MRI or perfusion imaging and is recommended in clinical guidelines. However, access to advanced imaging techniques is often scarce. We aimed to determine whether thrombolytic treatment with intravenous tenecteplase given within 4·5 h of awakening improves functional outcome in patients with ischaemic wake-up stroke selected using non-contrast CT.

Methods TWIST was an investigator-initiated, multicentre, open-label, randomised controlled trial with blinded endpoint assessment, conducted at 77 hospitals in ten countries. We included patients aged 18 years or older with acute ischaemic stroke symptoms upon awakening, limb weakness, a National Institutes of Health Stroke Scale (NIHSS) score of 3 or higher or aphasia, a non-contrast CT examination of the head, and the ability to receive tenecteplase within 4·5 h of awakening. Patients were randomly assigned (1:1) to either a single intravenous bolus of tenecteplase 0·25 mg per kg of bodyweight (maximum 25 mg) or control (no thrombolysis) using a central, web-based, computer-generated randomisation schedule. Trained research personnel, who conducted telephone interviews at 90 days (follow-up), were masked to treatment allocation. Clinical assessments were performed on day 1 (at baseline) and day 7 of hospital admission (or at discharge, whichever occurred first). The primary outcome was functional outcome assessed by the modified Rankin Scale (mRS) at 90 days and analysed using ordinal logistic regression in the intention-to-treat population. This trial is registered with EudraCT (2014-000096-80), ClinicalTrials.gov (NCT03181360), and ISRCTN (10601890).

Findings From June 12, 2017, to Sept 30, 2021, 578 of the required 600 patients were enrolled (288 randomly assigned to the tenecteplase group and 290 to the control group [intention-to-treat population]). The median age of participants was 73·7 years (IQR 65·9–81·1). 332 (57%) of 578 participants were male and 246 (43%) were female. Treatment with tenecteplase was not associated with better functional outcome, according to mRS score at 90 days (adjusted OR 1·18, 95% CI 0·88–1·58; p=0·27). Mortality at 90 days did not significantly differ between treatment groups (28 [10%] patients in the tenecteplase group and 23 [8%] in the control group; adjusted HR 1·29, 95% CI 0·74–2·26; p=0·37). Symptomatic intracranial haemorrhage occurred in six (2%) patients in the tenecteplase group versus three (1%) in the control group (adjusted OR 2·17, 95% CI 0·53–8·87; p=0·28), whereas any intracranial haemorrhage occurred in 33 (11%) versus 30 (10%) patients (adjusted OR 1·14, 0·67–1·94; p=0·64).

Interpretation In patients with wake-up stroke selected with non-contrast CT, treatment with tenecteplase was not associated with better functional outcome at 90 days. The number of symptomatic haemorrhages and any intracranial haemorrhages in both treatment groups was similar to findings from previous trials of wake-up stroke patients selected using advanced imaging. Current evidence does not support treatment with tenecteplase in patients selected with non-contrast CT.

AUTRES PISTES THERAPEUTIQUES

Thrombolytiques 3ème génération	Pro Urokinase	PROST (non inferiority mRS 0-1)
	Staphylokinase	Used in Russia
Anti GPIIb/IIIa	Eptifibatide Tirofiban	ON GOING
Antithrombine	Argatroban	
Anti GPVI	Glenzocimab	≃
Dispositifs	Hypothermia	↘
	Ultrasound	↘
	Gaz	↘
	Pre conditioning	ON GOING

ACTICOR BIOTECH

Suggère ↗ recanalisation

GLENZOCIMAB, A NOVEL ANTITHROMBOTIC, SHOWS FAVORABLE SAFETY PROFILE IN A SYSTEMATIC REVIEW OF DATA WITHIN THE CLINICAL DEVELOPMENT PROGRAM

Comenducci A.[1], Pletan Y.[1], Meilhoc A.[1], Sari A.[1], Desort-Henin V.[1], Toledano E.[1], Binay S.[1], Gharakhanian S.[1], Avenard G.[1]
[1] Acticor Biotech, Paris – France

INTRODUCTION

Glenzocimab, a novel humanized monoclonal antibody fragment targeting platelet GPVI[1-2], is now in late clinical development. We reviewed herein its safety profile following an uneventful phase I study[3], and the recent completion of two phase 2 RCTs: ACTIMIS study in patients with acute ischemic stroke[4] & GARDEN study in patients with SARS-Cov-2-induced acute respiratory distress syndrome[5].

METHOD

ACTIMIS Study Design

Phase 1b
60 patients recruited
(48 glenzocimab, 12 placebo)

125 mg | 250 mg | 500 mg | 1 000 mg

Phase 2a
100 patients recruited
(54 glenzocimab, 52 placebo)

1000 mg | placebo

Primary End Point
- Safety: serious adverse events (SAE), intracerebral hemorrhage (ICH)

Timeline
FPI: March 2019
LPI: June 2021

GARDEN Study Design

60 patients

1000 mg | placebo

3 days of treatment

2 countries:

Safety End Point
- Safety as key secondary endpoint.

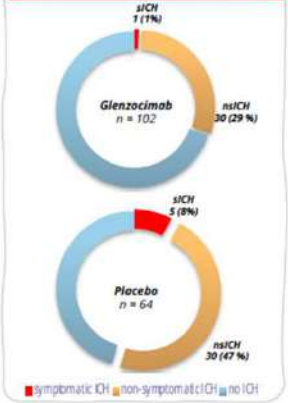
Timeline
FPI: December 2020
LPI: June 2021

ACTIMIS RESULTS

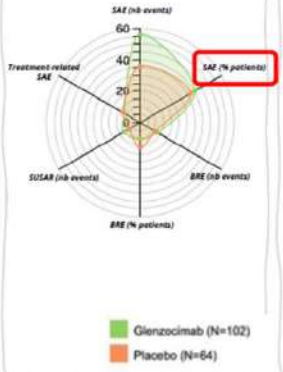
166 patients in the Safety Set

ACTIMIS reached its primary endpoint showing a favorable safety profile.

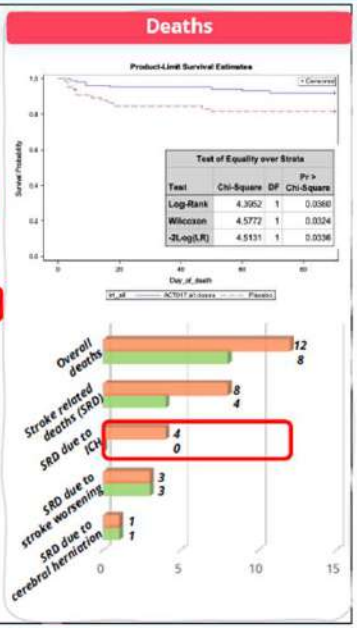
IntraCranial Hemorrhages



Adverse Events



Deaths



GARDEN RESULTS

61 patients in the Safety Set

SAFETY

- No death
- No SUSAR
- 31 SAE
  Not treatment related

Bleeding-Related Events (BRE)

- 2 serious BREs: disseminated intravascular coagulations. 1 *BRE related to treatment: petechiae*
- Comedication with LMWH without higher hemorrhagic risk.

TAKE HOME MESSAGES

- Documented safety results with 1000 mg (AIS patients) up to 3000 mg (ARDS patients) of glenzocimab IV administration.
- In AIS patients: Unexpected reduction of ICH incidence coupled with a subsequent mortality decrease, was a major result.
- In ARDS patients: Repeated treatment of 1000mg/day for 3 consecutive days showed a very favorable safety profile.

CONCLUSION

- **Targeting GPVI with glenzocimab does not increase the hemorrhagic risk at efficient dose for complete platelet aggregation inhibition. This is testified by the very low incidence of bleedings in both studies.**
- **Glenzocimab safety data suggest its clinical development plan can be safely continued without any specific warning nor limitation.**
- **Two ongoing phase 2/3 RCTs in AIS, ACTISAVE & GREEN[6] efficacy studies have a secondary aim to consolidate the favorable safety profile.**

World Stroke Organization
14TH WORLD STROKE CONGRESS
OCTOBER 26-29 SINGAPORE & ONLINE

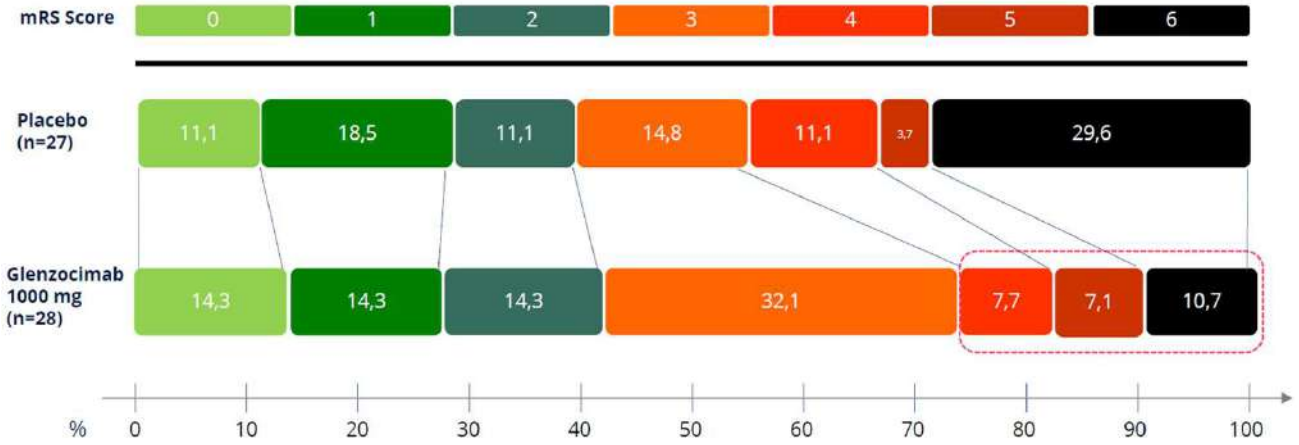
Abstract # 1631

1. Lebozec K. et al. MABS 2017,
2. Shaik N.F. et al. Blood Advances, 2021
3. Voors-Pette C. et al. ATVB 2019,
4. Mazhigi M. et al, ESOC Conference 2022,
5. Pottecher J. et al, ERS Congress 2022,
6. RHU BOOSTER BOOSTER anr

ACTICOR BIOTECH

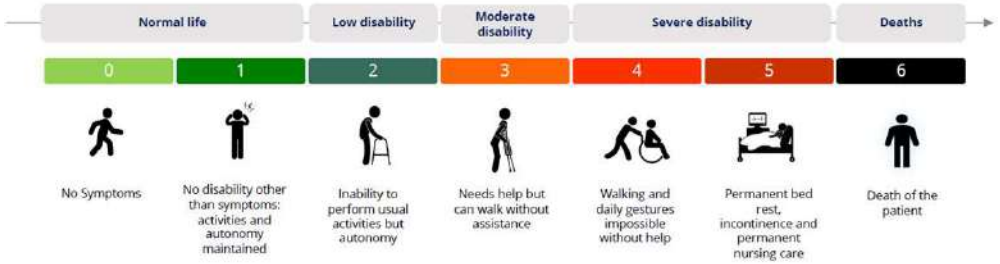
ACTICOR BIOTECH

Efficacy: mRS score at day 90 in alteplase + thrombectomy patients glenzocimab 1000 mg (n= 28) / placebo (n=27)



Glenzocimab results in a reduction in severe disability in patients undergoing thrombectomy

Efficacy : the mRS score assesses the level of disability



POUR QUI ?

THROMBOLYSE INTRA ARTERIELLE

RESCUE < TICI 2B > NO REFLOW

Original Contribution

December 1, 1999

Intra-arterial Prourokinase for Acute Ischemic Stroke

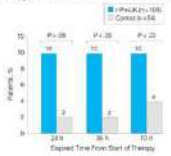
The PROACT II Study: A Randomized Controlled Trial

Anthony Furlan, MD; Randall Higashida, MD; Lawrence Wechsler, MD; et al

» Author Affiliations

JAMA. 1999;282(21):2003-2011. doi:10.1001/jama.282.21.2003

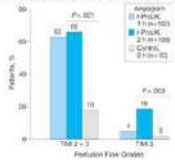
Figure 4. Intracranial Hemorrhage With Neurological Deterioration in Patients Treated as Randomized



HCS ↗

Data are based on adjudicated results by an external safety committee blinded to treatment and clinical outcome. Neurological deterioration was defined as a 4-point or more increase on the total National Institutes of Health Stroke Scale (NIHSS) score or a 1-point increase in level of consciousness on the NIHSS. Timepoints were based on the onset of symptoms relative to the initiation of randomized therapy. r-proUK indicates recombinant prourokinase.

Figure 5. Recanalization of Occluded Middle Cerebral Artery in Patients Treated as Randomized



TICI ↗

Determination of 2-hour recanalization was made by a neuroradiologist at a core facility who was blinded to treatment and clinical outcome. One-hour recanalization was determined unblinded by the neuroradiologist. TIMI indicates Thrombolysis in Myocardial Infarction trial. TIMI 2 is partial flow in the middle cerebral artery; TIMI 3 is complete flow in both the M_1 and M_2 segments of the middle cerebral artery.

Figure 3. Distribution of NIHSS-Stratum Adjusted Modified Rankin Scores at 90-Day Follow-up Assessment

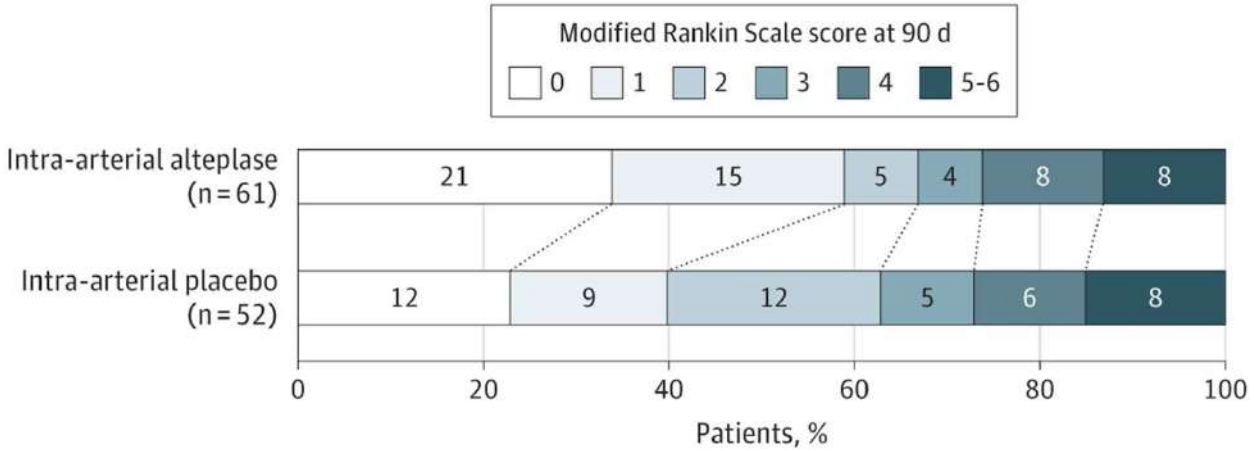
OUTCOME ↗

A score of ≤2 (yellow) on the modified Rankin scale (mRS) indicates a favorable outcome of slight or no disability. A score of 6 represents death. r-proUK indicates recombinant prourokinase.

February 10, 2022

Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke

The CHOICE Randomized Clinical Trial



mRS1 ↗

CONCLUSIONS

INTERÊT DE LA TIV → NVX AGENTS THROMBOLYTIQUES

DRIP AND SHIP

MOTHERSHIP

	ALTEPLASE (0,9 mg/kg)	TENECTEPLASE (0,25 mg/kg)
TIV < 4,5H	✓	✓
TIV > 4,5H (WAKE-UP, EXTEND IV)	✓	✗