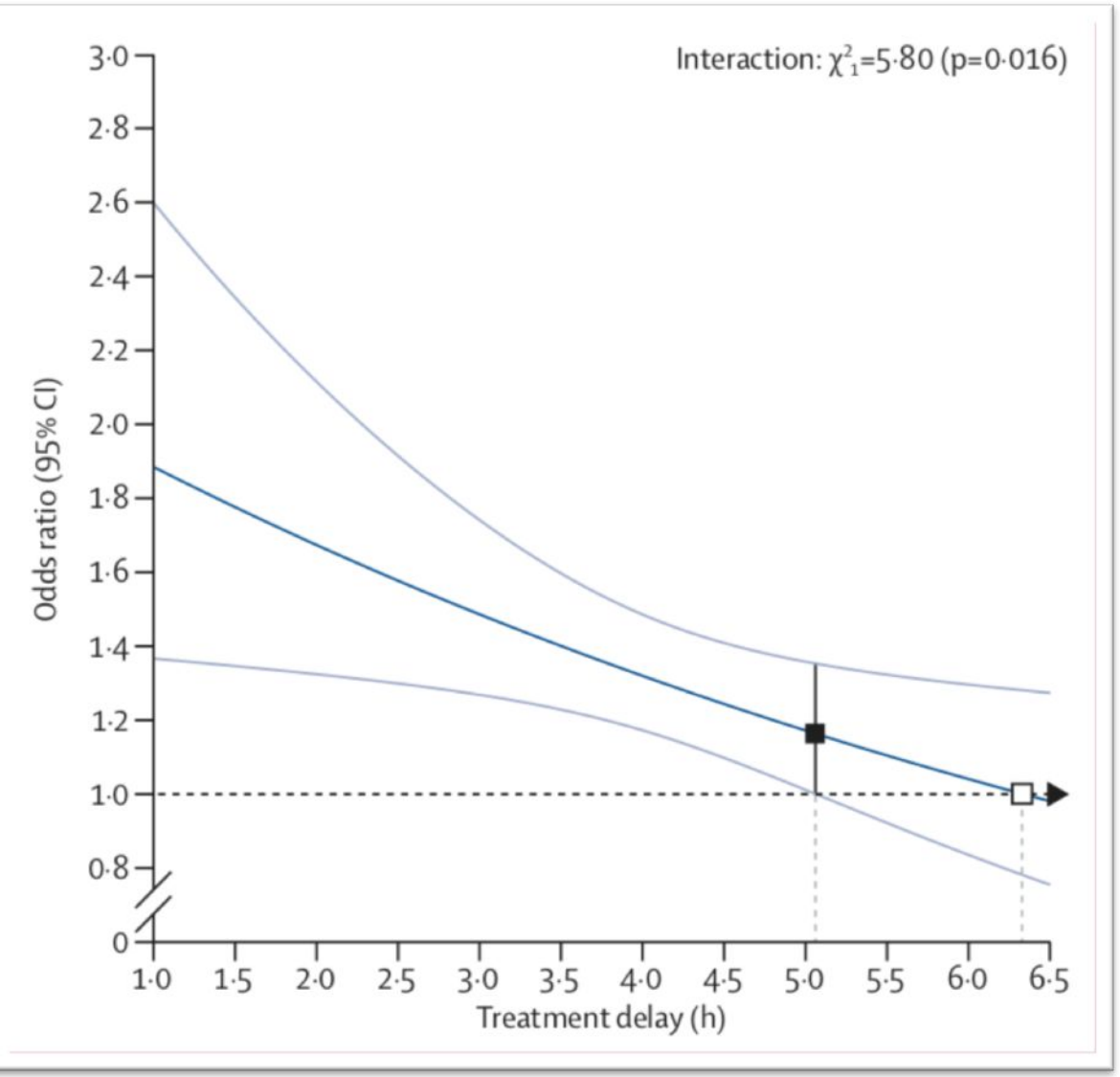
Thrombolyse en fenêtre tardive

Présenté par Marilyn Labrie,

Neurologue spécialisée en neurologie vasculaire Hôtel-Dieu de Lévis

Conflits d’intérêts

- Aucun



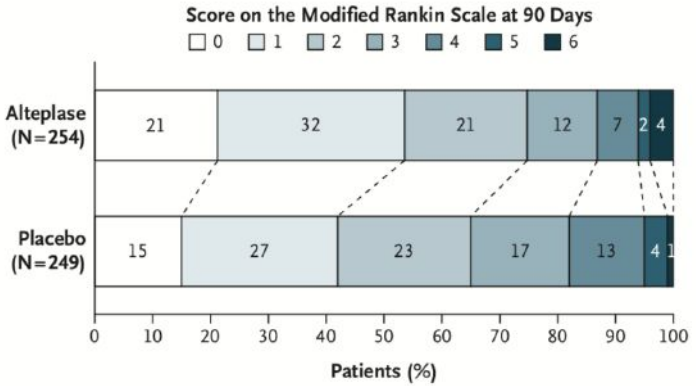
***Lancet* 2014; 384: 1929–35**

Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; **378:** 11–21.
Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; **378:** 708–18.

ORIGINAL ARTICLE

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*



Thomalla G, Simonsen CZ, Boutitie F, et al. MRIguided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018; **379:** 611–22.

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, C.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*

EXTEND

RCT

TPA IV pour les AVC en fenêtre tardive (4,5 – 9 h ou au réveil) sélectionnés par imagerie de perfusion serait bénéfique

Terminée précocément suite à la publication de Wake-up

EXTEND

Critères d'inclusion

>= 18ans, mRS < 2, NIHSS 4 à 26

Pénombre détectée à l'imagerie de perfusion automatisée (TDM ou IRM de perfusion)

- Mismatch de 1,2
- Différence absolue > 10 cc
- Core ischémique < 70 cc

Non éligible si thrombectomie considérée

Intervention

TPA versus placebo

Issue primaire

- mRS 0-1 à 90 jours

Issues secondaires

- Analyse ordinale des mRS
- mRS 0-2 à 90 jours
- % de reperfusion à 21 heures

Issues tertinaires

- Recanalisation à 24 heures (TICI 2-3)
- Amélioration neurologique majeure à 24h

Sécurité

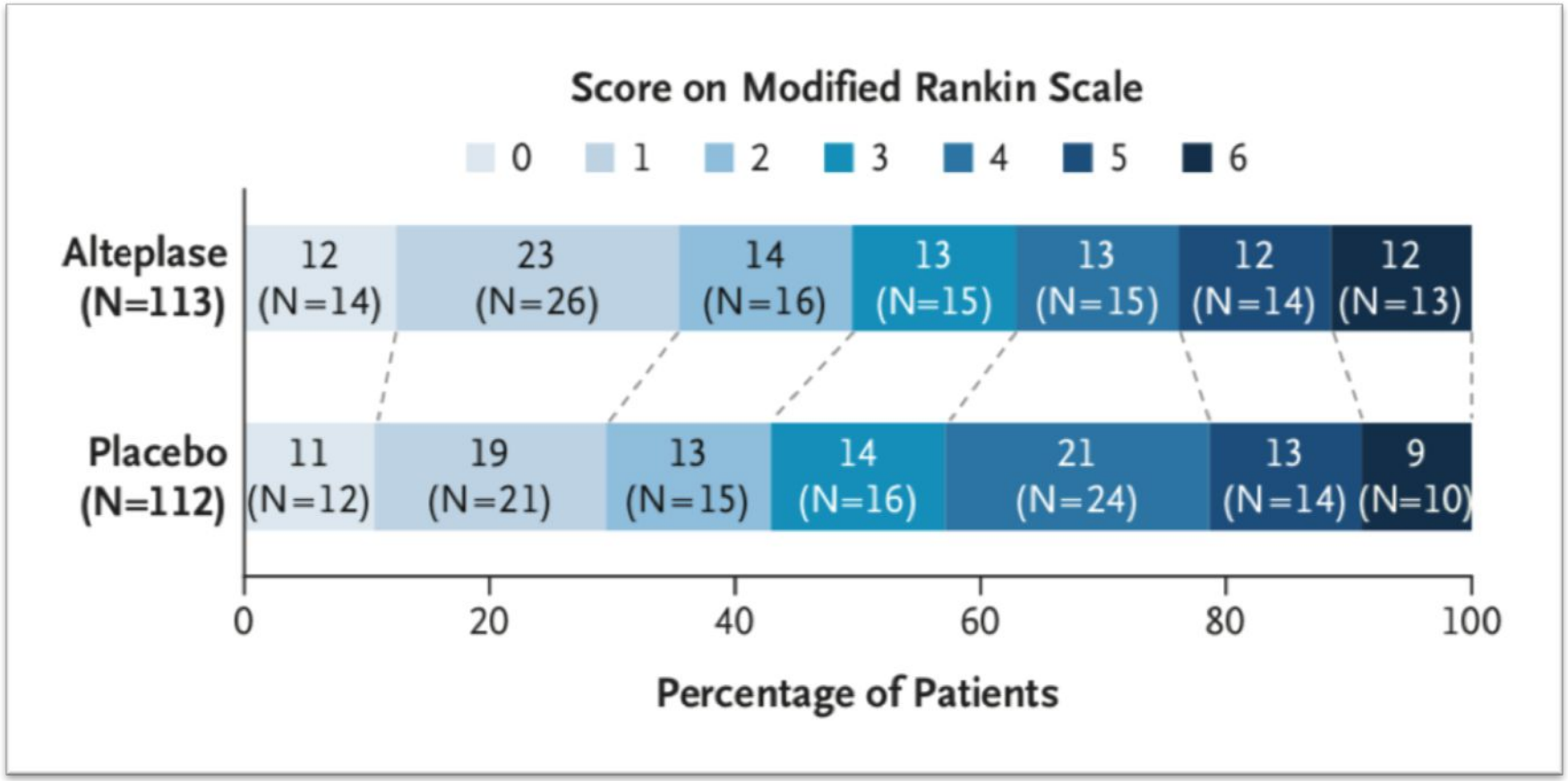
- Décès < 90 jours
- Hémorragie intracrânienne symptomatique (PH2 < 36 heures post intervention + détérioration neurologique)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Alteplase (N = 113)	Placebo (N = 112)
Age — yr	73.7±11.7	71.0±12.7
Male sex — no. (%)	59 (52.2)	66 (58.9)
Median NIHSS score (IQR)†	12.0 (8.0–17.0)	10.0 (6.0–16.5)
Clinical history of atrial fibrillation — no. (%)	46 (40.7)	36 (32.1)
Geographic region — no. (%)		
Australia, New Zealand, and Finland	90 (79.6)	88 (78.6)
Taiwan	23 (20.4)	24 (21.4)
Time from stroke onset to randomization — no. (%)		
>4.5 to 6.0 hr	12 (10.6)	11 (9.8)
>6.0 to 9.0 hr	28 (24.8)	28 (25.0)
Awoke with stroke symptoms‡	73 (64.6)	73 (65.2)
Median time from stroke onset to hospital arrival (IQR) — min	308 (227–362)	293 (230–357)
Median time from stroke onset to initiation of intravenous therapy (IQR) — min	432 (374–488)	450 (374–500)
Median time from hospital arrival to initiation of intravenous therapy (IQR) — min	124 (81–179)	127 (87–171)
Imaging result		
Large-vessel occlusion — no.(%)§	78 (69.0)	81 (72.3)
Median volume of irreversibly injured ischemic-core tissue at initial imaging (IQR) — ml¶	4.6 (0–23.2)	2.4 (0–19.5)
Median perfusion-lesion volume at initial imaging (IQR) — ml‖	74.3 (40.1–134.0)	78 (47.7–111.8)

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)	


Score on Modified Rankin Scale
0
1
2
3
4
5
6
Alteplase (N=113)
12 (N=14)
23 (N=26)
14 (N=16)
13 (N=15)
13 (N=15)
12 (N=14)
12 (N=13)
Placebo (N=112)
11 (N=12)
19 (N=21)
13 (N=15)
14 (N=16)
21 (N=24)
13 (N=14)
9 (N=10)
0
20
40
60
80
100
Percentage of Patients

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

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‡*

Méta-analyse

- Objectif : Déterminer l'efficacité de la thrombolyse en fenêtre tardive (4,5–9 heures) lorsque guidée par imagerie de perfusion
- Revue systématique et méta-analyse des données individuelles de patients
- Critères d'éligibilité :
  - Études de TPA versus placebo chez patients avec AVC ischémique traité 4,5-9h versus AVC au réveil, imagé par études de perfusion (TDM ou IRM)
- Issue primaire :
  - Excellent outcome fonctionnel (mRS 0-1 à 3 mois)
- Outcome de sécurité :
  - Décès et hémorragie asymptomatique

3 études satisfaisant les critères d'éligibilité

- **EXTEND ;**
- **ECASS4-EXTEND** mêmes critères d'inclusion clinique que EXTEND, sélectionnés par IRM perfusion, non automatisée. Terminée précocement secondairement à un pauvre recrutement ;
- **EPITHET phase 2** AVC 3-6hrs sélectionnés par IRM perfusion non automatisée.

	Placebo (n=201)	Alteplase (n=213)
Age, years	72·0 (12·3)	73·2 (12·2)
Sex		
Men	116 (58%)	119 (56%)
Women	85 (42%)	94 (44%)
NIHSS score	10 (6–16)	12 (7–17)
Previously diagnosed atrial fibrillation	63 (31%)	79 (37%)
History of hypertension	134 (67%)	159 (75%)
History of diabetes	41 (20%)	49 (23%)
History of smoking	62/165 (38%)	58/179 (32%)
Geographical region		
Australia or New Zealand	110 (55%)	121 (57%)
Europe	67 (33%)	69 (32%)
Asia	24 (12%)	23 (11%)
Time from stroke onset to randomisation		
>4·5–6·0 h	49 (24%)	58 (27%)
>6·0–9·0 h	48 (24%)	50 (24%)
Wake-up stroke	104 (52%)	105 (49%)
Imaged with CT perfusion	96 (48%)	100 (47%)
Imaged with perfusion-diffusion MRI	105 (52%)	113 (53%)
Time from stroke onset* to initiation of intravenous therapy, min	413 (353–480)	417 (346–485)
Time from last known to be well to initiation of intravenous therapy, min	487 (360–655)	471 (355–649)
Large vessel occlusion	122/198 (62%)	124/205 (60%)
Ischaemic core volume† at initial imaging	8·1 (0–20·4)	8·0 (0–25·3)
Perfusion lesion volume‡ at initial imaging	64·3 (33·2–97·0)	63·9 (27·9–117·2)

Data are mean (SD), n (%), median (IQR), or n/N (%). NIHSS=National Institutes of Health Stroke Scale. *Onset time measured as the midpoint of falling asleep and waking with stroke symptoms for patients with wake-up stroke. †Relative cerebral blood flow less than 30% of normal blood flow. ‡Time to maximum >6 s.

Table 1: **Baseline characteristics of all patients**

	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**

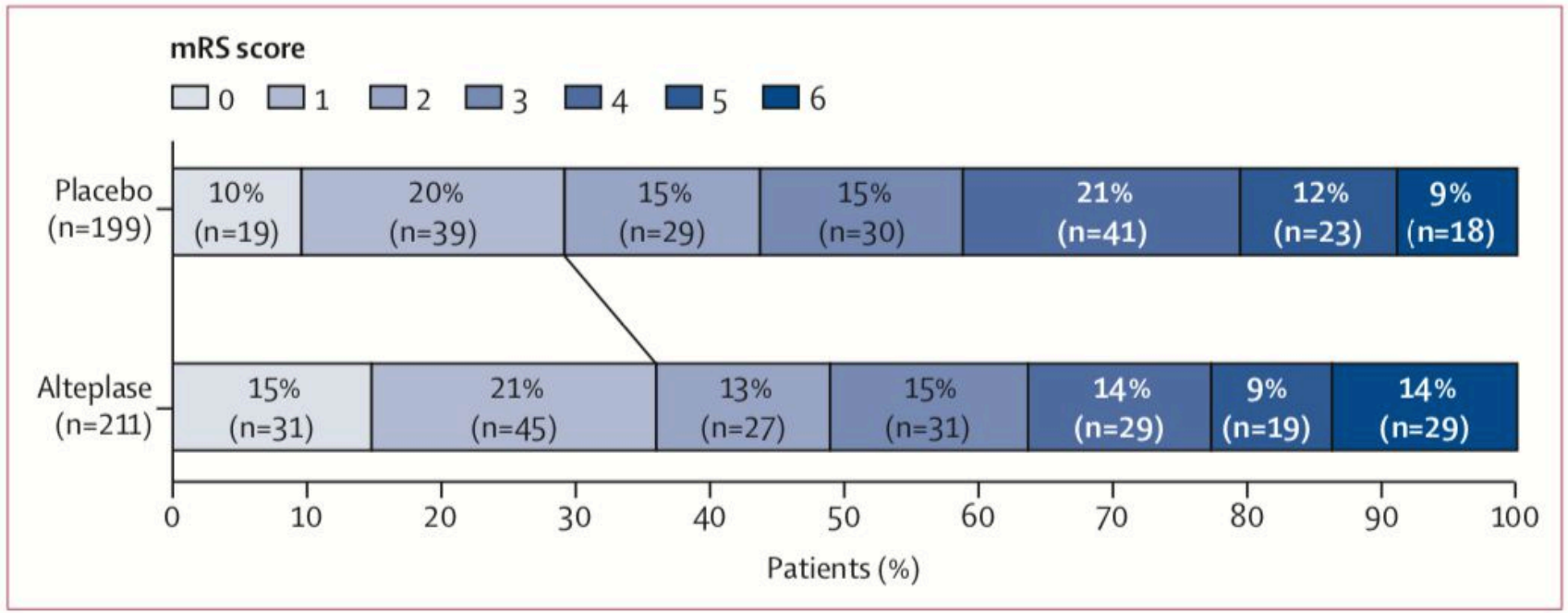


Figure 1: **mRS scores at 3 months for all patients**

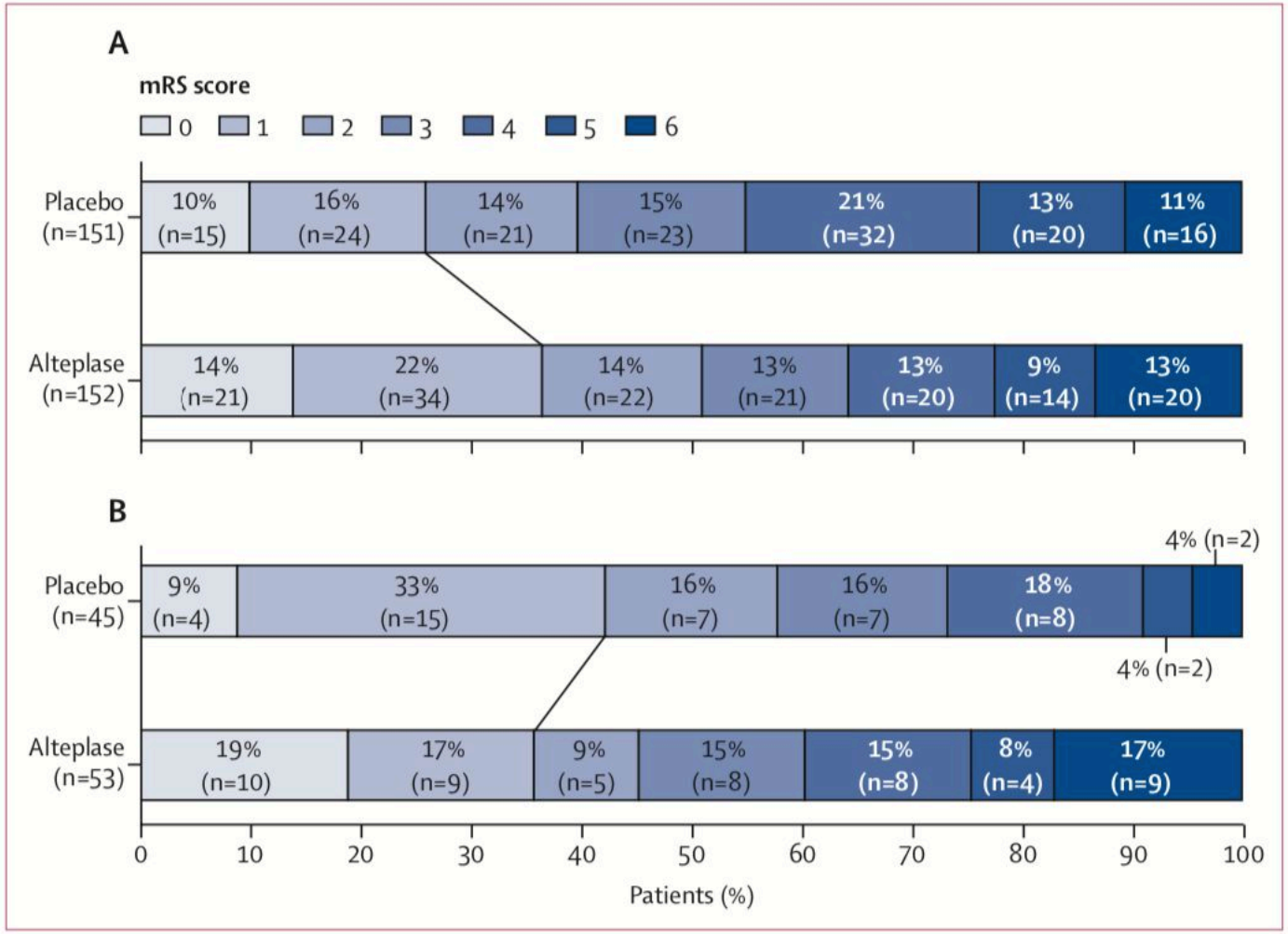


***Figure 3*: mRS score at 3 months by perfusion mismatch subgroup**

mRS score for patients with automated perfusion mismatch (A), and patients without automated perfusion mismatch (B). Among patients with mismatch, one patient in the placebo group was excluded because they did not have mRS assessment at 3 months. Among patients without mismatch, one patient in the placebo group and two patients in the alteplase group were excluded because they did not have mRS assessment at 3 months. Imaging data were not available for six patients in the alteplase group and three patients in the placebo group; thus perfusion mismatch status could not be determined. mRS=modified Rankin Scale.