La richiesta di competenza
neurologica nel prossimo futuro
Roma 1 Marzo 2019

Gestione dell'ictus al risveglio

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Disclosures

- Advisory Board, presentazioni a congresso, workshops
  - Abbott
  - Bayer
  - Boehringer Ingelheim
  - Bristol Myers Squibb
  - Daiichi Sankyo
  - Medtronic
  - Pfizer-BMS

- Unrestricted research grant
  - Boehringer Ingelheim

Di cosa parleremo

- Ictus al risveglio:

- Trombolisi intravenosa

- Trombectomia meccanica

Di cosa parleremo

- Ictus al risveglio:

- Trombolisi intravenosa

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2018 Aug 16;379(7):611-622

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*

BACKGROUND

Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase.

METHODS

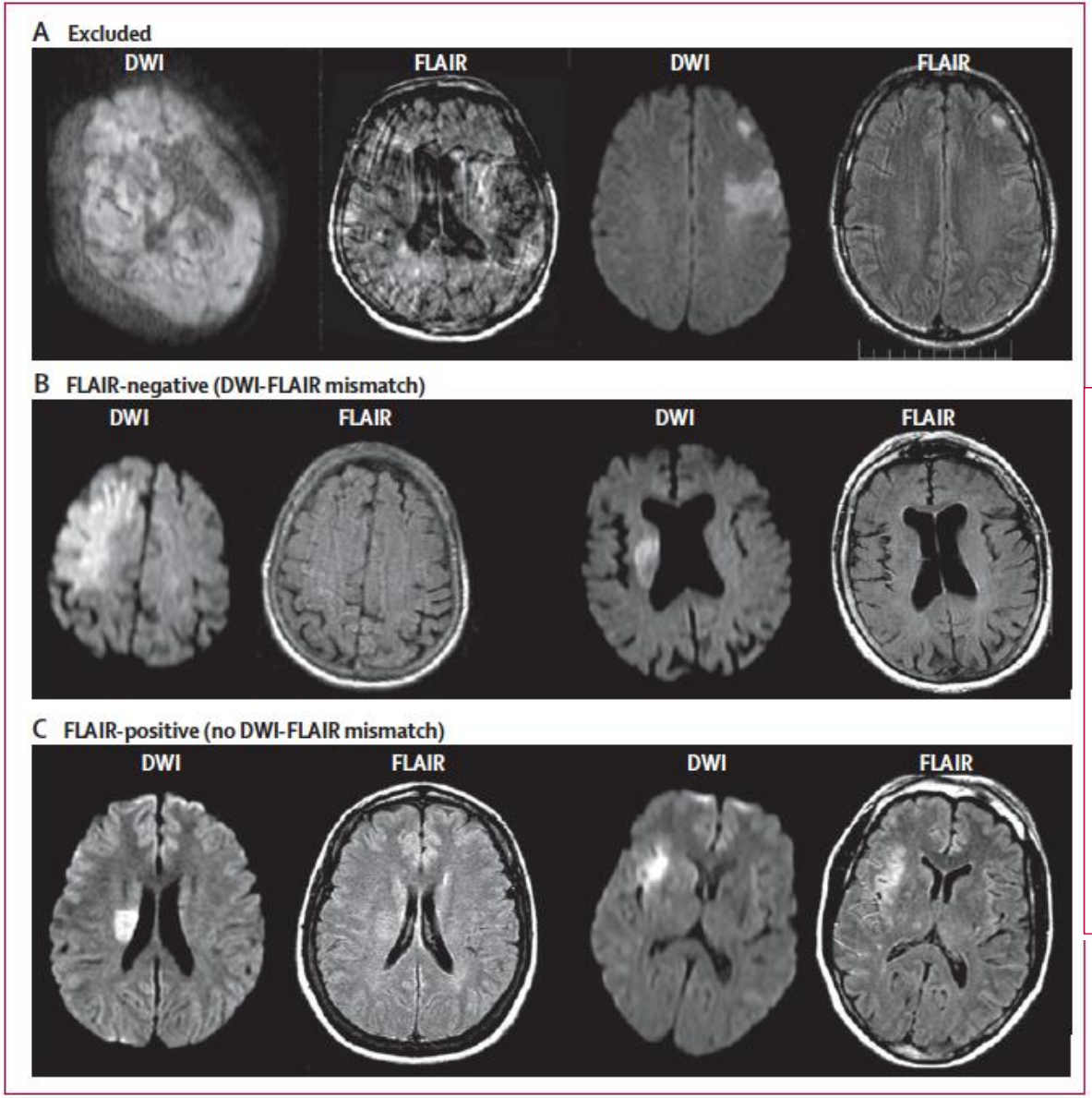
In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. We excluded patients for whom thrombectomy was planned. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis).

RESULTS

The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P=0.003). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P=0.15).

CONCLUSIONS

In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days. (Funded by the European Union Seventh Framework Program; WAKE-UP ClinicalTrials.gov number, NCT01525290; and EudraCT number, 2011-005906-32.)



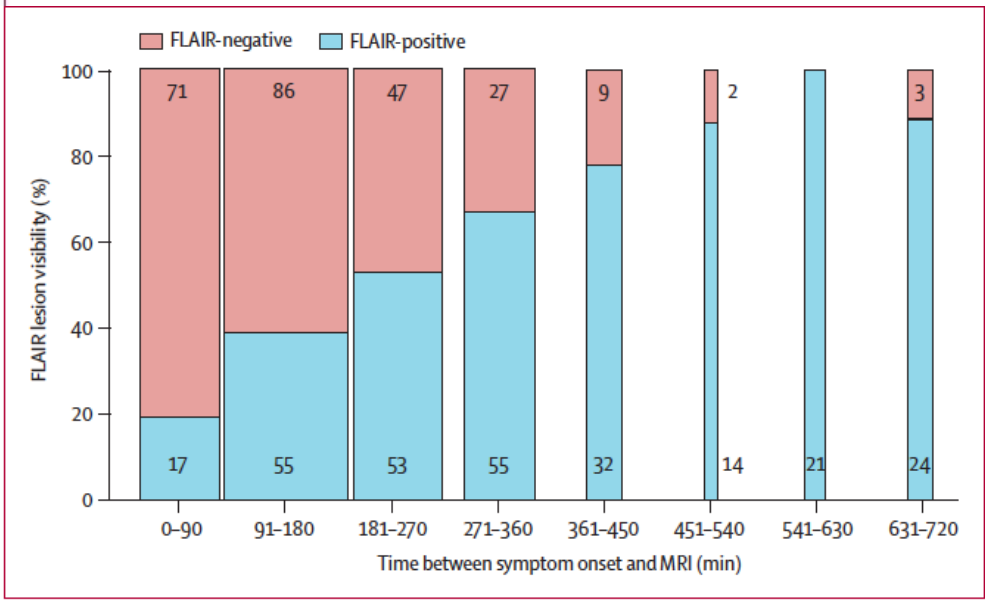
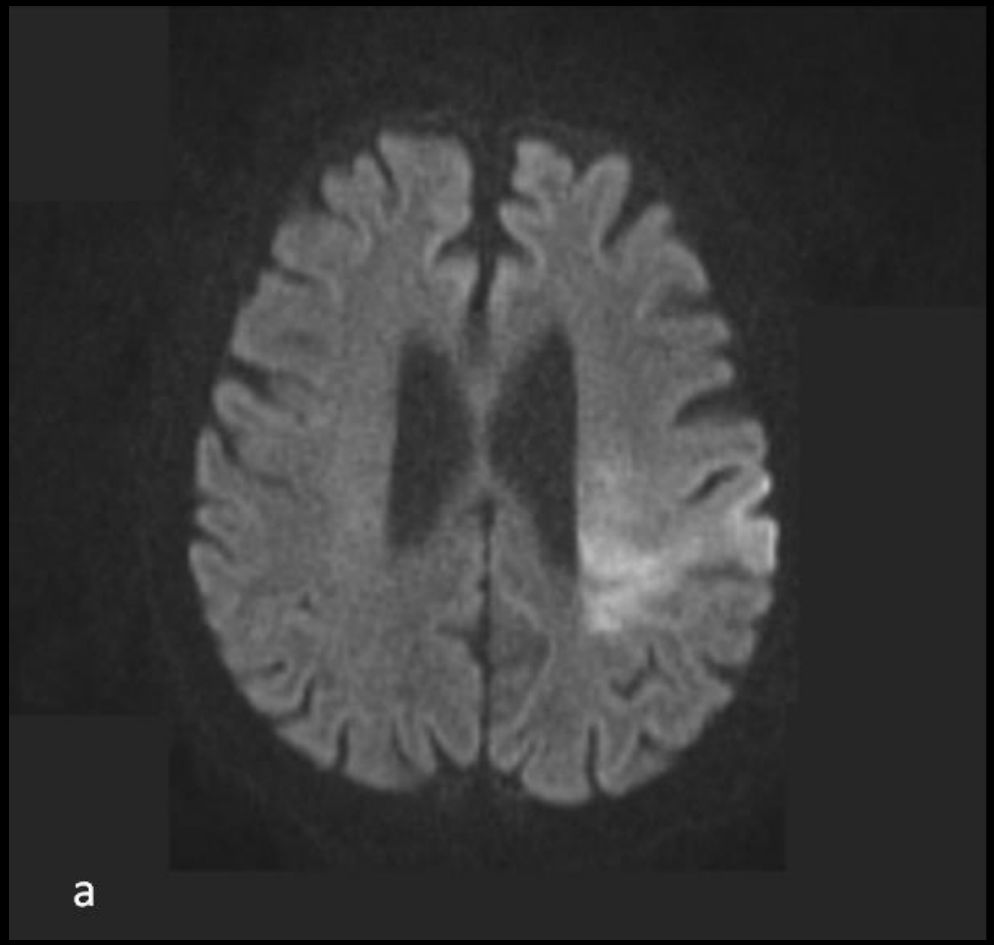


Figure 2: **Examples of DWI and FLAIR images**
(A) Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) images excluded from the final analysis because of poor quality (left) or the presence of multiple acute and subacute ischaemic lesions of different ages, precluding the attribution of symptom onset to one specific lesion (right). (B) Pairs of images showing acute ischaemic lesions on DWI but not on FLAIR imaging (FLAIR-negative, DWI-FLAIR mismatch). (C) Pairs of images showing acute ischaemic lesions on DWI together with a corresponding subtle (left) or obvious (right) parenchymal hyperintensity on FLAIR imaging (FLAIR-positive, no DWI-FLAIR mismatch).

Tomalla G et al, Lancet Neurol 2011

MR - DWI



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MR - FLAIR

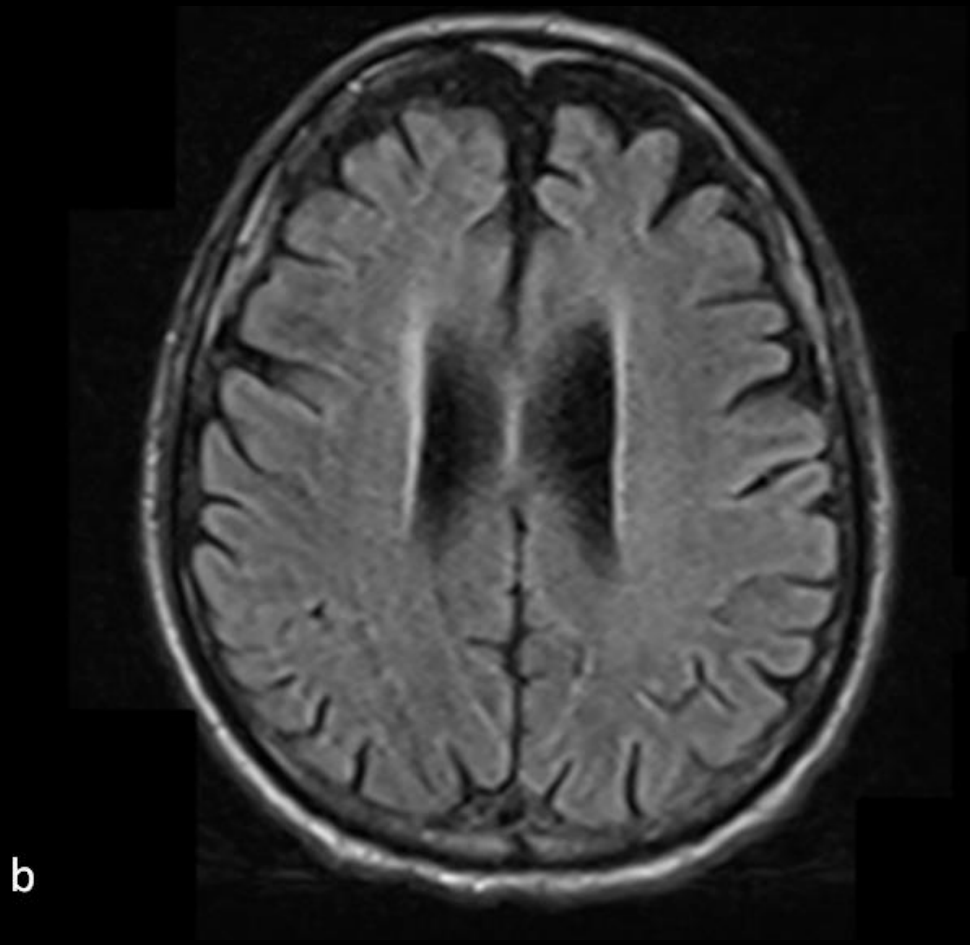

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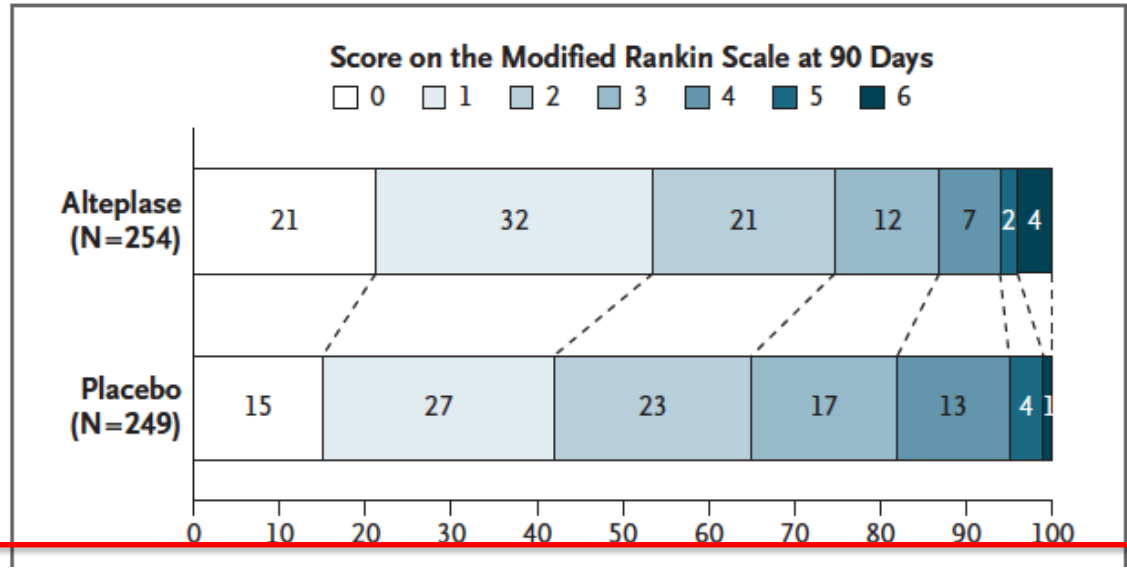
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

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)



In conclusion, among patients with acute stroke and an unknown time of symptom onset who had MRI findings of an ischemic lesion on diffusion-weighted imaging but no parenchymal hyperintensity in the corresponding region on FLAIR, intravenous thrombolysis with alteplase resulted in a better functional outcome than treatment with placebo.

Table 3. Safety Outcom

Outcome			ed Odds atio % CI)*	P Value
Secondary				
Symptomatic intracrani				
As defined in SITS-M			.95 –42.87)	0.15
As defined in ECASS			.40 –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

Linee guida ISO-SPREAD Possibile nuova raccomandazione

~~**Raccomandazione 9.3 Debole a favore**~~

~~**Il trattamento con r-tPA e.v. è raccomandato in pazienti con ictus ad ora di insorgenza non nota o al risveglio, qualora le neuroimmagini avanzate (RM DW e PW o pTC) definiscano una zona di mismatch tessutale e/o consentano di datare l'evento almeno entro le 3 ore (confronto RM DW con RM FLAIR**~~

Raccomandazione Forte a favore

Il trattamento con r-tPA e.v. è raccomandato in pazienti con ictus al risveglio, qualora il confronto fra RM DW e FLAIR consenta di datare l'esordio dell'evento entro le 4.5 ore

Di cosa parleremo

- Ictus al risveglio:

- Trombectomia meccanica

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. Engl B.P. Mehta, B.W. Baxter, M.G. Abra F.R. Hellinger, L. Feng, J.F. Kirmani, D. V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik J.-M. Olivot, W.G. Tekle, R. Shields D.S. Liebeskind, J.L. Saver, and T.G. Jo

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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*

N Engl J Med 2018 Feb 22;378(8):708-718

DAWN

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N=107)		Control Group (N=99)	
Type of stroke onset — no. (%)‡				
On awakening	67 (63)	90%	47 (47)	85%
Unwitnessed stroke	29 (27)		38 (38)	
Witnessed stroke	11 (10)		14 (14)	

DEFUSE 3

Table 1. Baseline Characteristics of the Patients and Features of Thrombectomy.*

Characteristic	Endovascular Therapy (N=92)		Medical Therapy (N=90)	
Stroke onset witnessed — no. (%)				
Yes‡	31 (34)		35 (39)	
No				
Symptoms were present on awakening	49 (53)	66%	42 (47)	61%
Symptoms began during wakefulness	12 (13)		13 (14)	

Linee guida ISO-SPREAD
Possibile raccommandazione

Raccomandazione **Debole a favore**

Le tecniche di trombectomia meccanica sono indicate in pazienti con ictus ischemico da occlusione della carotide interna intracranica o del tratto prossimale dell'arteria cerebrale media, esordito da 6 a 24 ore dall'ultima volta in cui sono stati visti in condizione di normalità, in presenza di una delle seguenti condizioni:

- **età ≥ 80 anni, punteggio NIHSS ≥10 e volume infartuale < 21 ml**
- **età < 80 anni, punteggio NIHSS ≥10 e volume infartuale <31 ml**
- **età < 80 anni, punteggio NIHSS ≥20 e volume infartuale fra 31 e 51 ml**

Il volume infartuale va valutato con risonanza magnetica con sequenze in diffusione (RM DW) o con TC di perfusione (pTC) e calcolato con un software automatico.

Linee guida ISO-SPREAD
Possibile raccommandazione

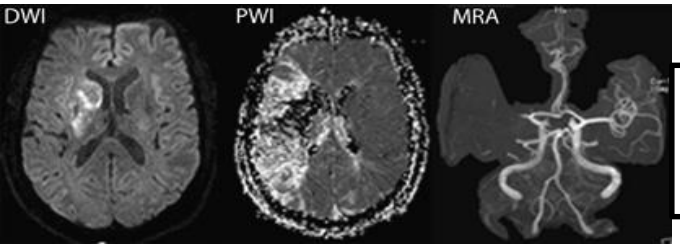
Raccomandazione **Debole a favore**

Le tecniche di trombectomia meccanica sono indicate in pazienti con ictus ischemico da occlusione della carotide interna intracranica o del tratto prossimale dell'arteria cerebrale media, esordito da 6 a 16 ore dall'ultima volta in cui sono stati visti in condizione di normalità, in presenza di tutte le seguenti condizioni:

- **volume basale dell'infarto inferiore a 70 ml**
- **rapporto volumetrico fra area di ipoperfusione e area infartuale ≥1.8**
- **volume di ischemia potenzialmente reversibile ≥ 15 ml**

Volume infartuale basale e volume dell'area ipoperfusa vanno valutati con risonanza magnetica con sequenze in diffusione e perfusione (RM DW/PW) o con TC di perfusione (pTC) e calcolati con un software automatico

Pz con ictus al risveglio o che giunge in DEA tra le 6 le 24 h dall'ultima volta che è stato visto in buona salute



MRI DW/PW + Angio-MRA

Ictus Ischemico

WAKE-UP STROKE TRIAL

18-80 aa
FLAIR -
DWI + <1/3 ACM
< ½ ACA o ACP
< 100 ml
ANGIO -

ANGIO +

Trombolisi ev

≥ 18 aa
FLAIR +
DWI +
ANGIO -

Nessun trattamento

DAWN TRIAL

Age ≥ 18 aa
FLAIR +
DWI +
ANGIO + (M1 o ICA)
MISMATCH DWI/Clinico -
Group A: ≥ 80 aa, NIHSS ≥ 10, core <21 cc
Group B: < 80 aa, NIHSS ≥ 10, core <31 cc
Group C: < 80 aa, NIHSS ≥ 20, core 31 to <51 cc
pre-Rankin 0-1

DEFUSE TRIAL

Age 18-85
Target mismatch (6-16h)
DW volume < 70 ml
PW Volume ≥15 ml
Mismatch Ratio ≥ 1.8
18-90 aa
NIHSS ≥ 6
pre-Rankin 0-2

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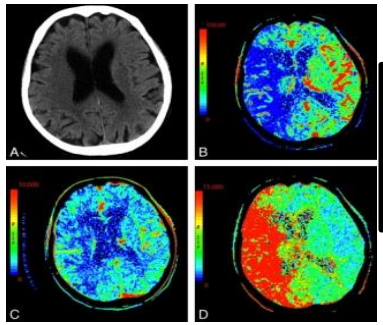
Trombectomia

Pz con ictus al risveglio o che giunge in DEA tra le 6 le 24 h dall'ultima volta che è stato visto in buona salute



TC + Angio-TC Multifasica
+TC perfusionale

Ictus Ischemico

DAWN TRIAL

Age ≥ 18 aa
Core <1/3 ACM
ANGIO + (M1 o ICA)
CTP-rCBF maps
Mismatch clinico/radiologico
Group A: ≥ 80 aa, NIHSS ≥ 10, core <21 cc
Group B: < 80 aa, NIHSS ≥ 10, core <31 cc
Group C: < 80 aa, NIHSS ≥ 20, core 31 to <51 cc
pre-Rankin 0-1

DEFUSE TRIAL

Age 18-85
Target mismatch (6-16h)
Ischemic core < 70 ml
Perfusion Volume ≥15 ml
Mismatch Ratio ≥ 1.8
18-85 aa
NIHSS ≥ 6
pre-Rankin 0-2

Trombectomia