Ruolo della RMN nell'Ictus Ischemico Acuto

Criteri WAKE-UP, ECASS IV, EXTEND, EPITHET, DAWN e DEFUSE 3

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ARNAS "G.Brotzu"

Cagliari

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Wake-UP Stroke Trial

Thomalla G, et al. 2018. 379(7):611-622

Inclusion Criteria

- Acute stroke with "last known normal" time > 4.5 hrs (no upper time limit)
- Treatment can be started within 4.5 hours of symptom recognition (e.g., awakening)
- Met standard eligibility criteria for the use of alteplase
- Had DWI-FLAIR mismatch (abnormal signal on DWI and no marked signal change on FLAIR in the region of the acute stroke).

- Excluded:
  - **Large strokes** > 1/3 of MCA or NIHSS > 25 or > 50% of the anterior cerebral artery (ACA) or posterior cerebral artery (PCA) territory (visual inspection) or > 100 ml
  - FLAIR showing a marked parenchymal hyperintensity in a region corresponding to the acute DWI lesion indicative of an acute ischemic lesion with a high likelihood of being > 4.5 hours old
  - Planned thrombectomy

The primary endpoint was mRS = 0-1 at 90 days

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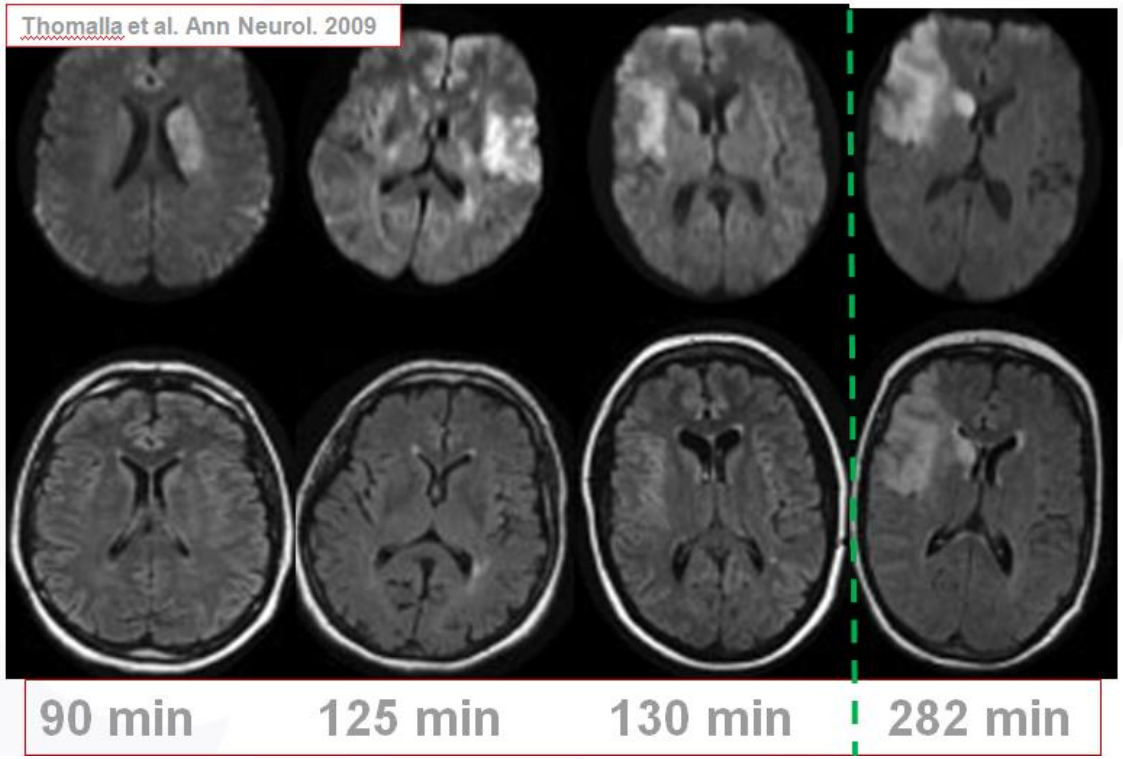
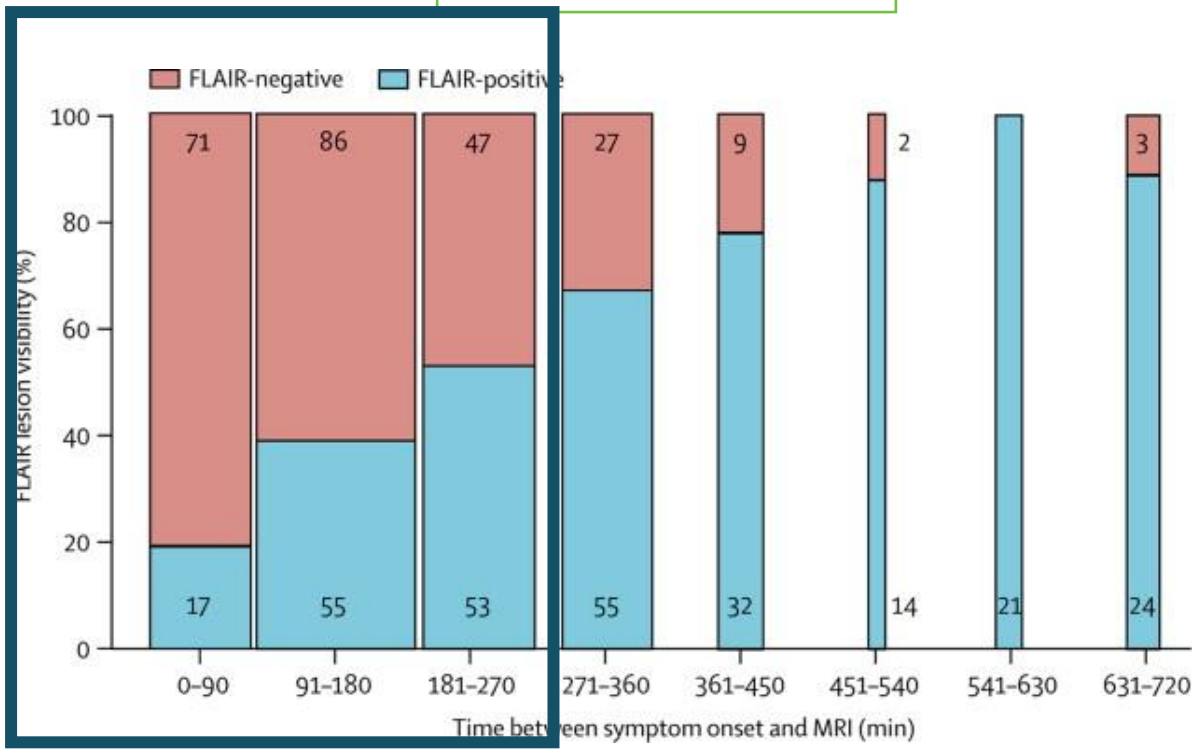
Positive DWI, Negative FLAIR may identify Strokes < 4.5 hours old



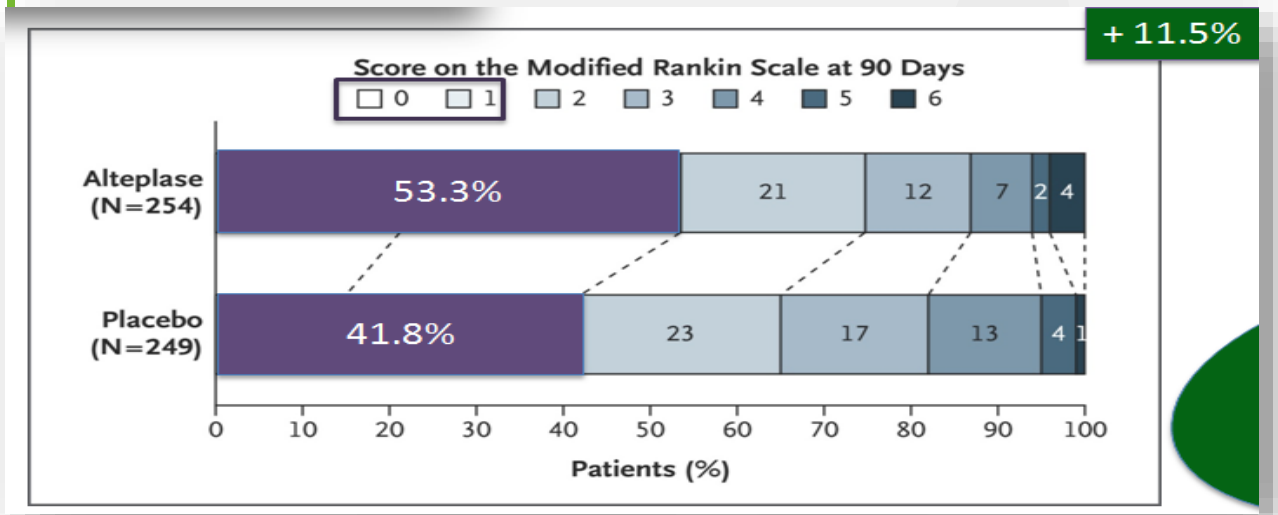
Thomalia et al Lancet Neurol 2011

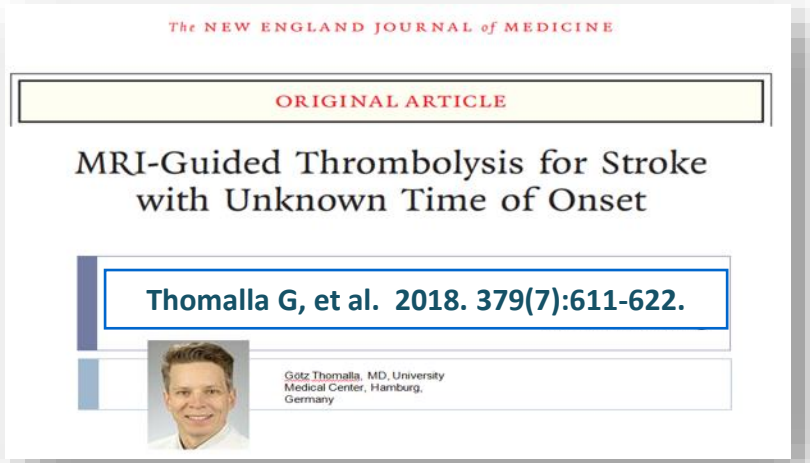


DWI-FLAIR mismatch identified patients within 4·5 h of symptom onset with

- ***62% (95% CI 57–67) sensitivity,***
- ***78% (72–84) specificity,***
- ***83% (79–88) positive predictive value,***
- ***54% (48–60) negative predictive value.***

WAKE-UP STUDY





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.

"Our trial provides evidence of benefit from reperfusion treatment with alteplase in patients with minor or moderate stroke who would not usually be eligible for endovascular treatment".

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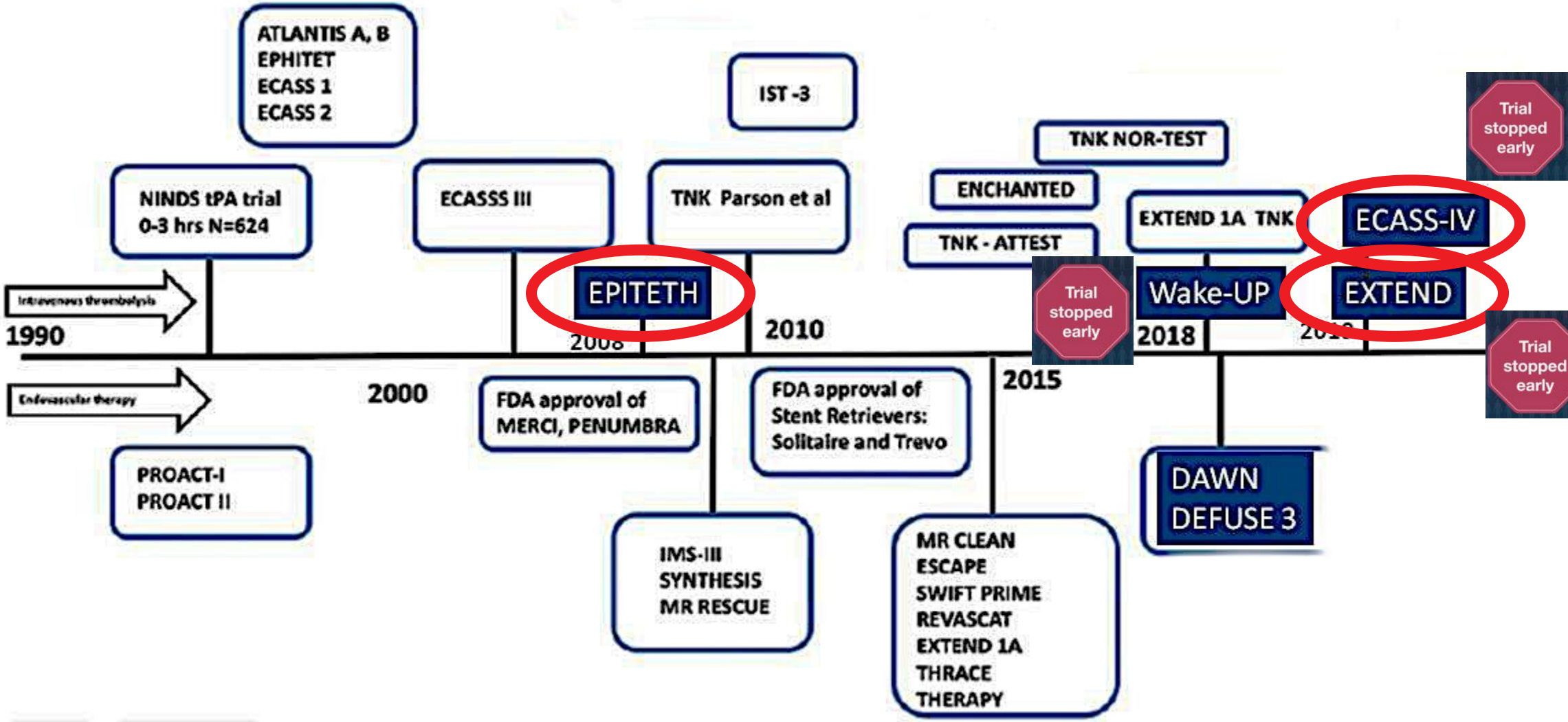
Wake-UP Stroke Trial

Criticisms

- Trial was stopped prematurely due to lack of funding
- Small number of patients with NIHSS >10, limiting generalizability to that group
- 20% of patients enrolled in the trial could have qualified for thrombectomy in DAWN and DEFUSE 3


ATLANTIS A, B
EPHITET
ECASS 1
ECASS 2
IST -3
TNK NOR-TEST
Trial stopped early
NINDS tPA trial
0-3 hrs N=624
ECASSS III
TNK Parson et al
ENCHANTED
EXTEND 1A TNK
ECASS-IV
TNK - ATTEST
EPITETH
Trial stopped early
Wake-UP
EXTEND
Intravenous thrombolysis
1990
2008
2010
2018
Trial stopped early
Endovascular therapy
2000
2015
FDA approval of MERCI, PENUMBRA
FDA approval of Stent Retrievers: Solitaire and Trevo
PROACT-I
PROACT II
DAWN
DEFUSE 3
IMS-III
SYNTHESIS
MR RESCUE
MR CLEAN
ESCAPE
SWIFT PRIME
REVASCAT
EXTEND 1A
THRACE
THERAPY

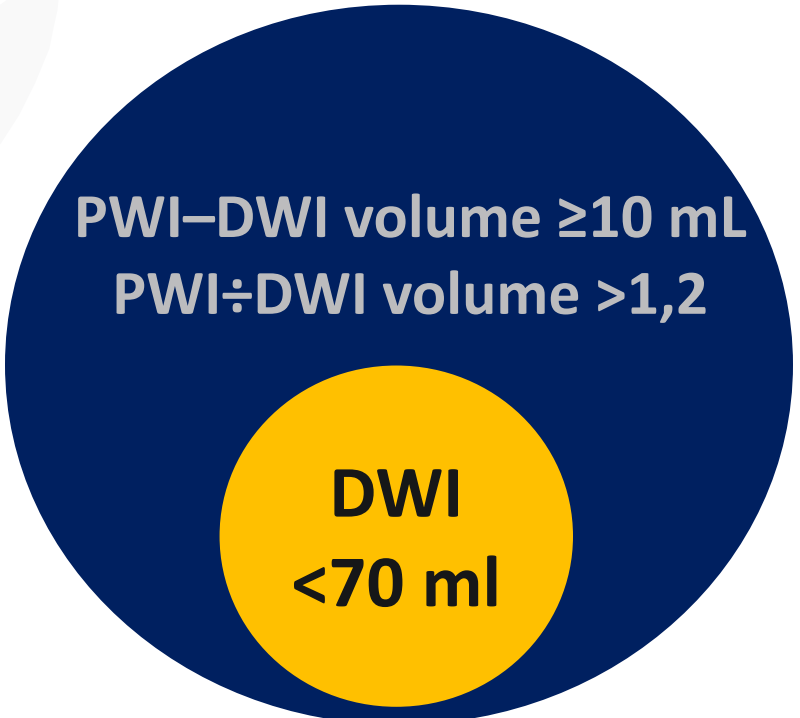
EPITHET Stroke Trial

Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)

Hypothesis

Alteplase given 3–6 h after stroke onset promotes reperfusion and attenuates infarct growth in patients who have a mismatch in perfusion-weighted MRI (PWI) and diffusion- weighted MRI (DWI)

- DWI at baseline and day 3–5 and T2-weighted lesions at day 90 were assessed by two independent raters who used standard planimetric software (Analyze 7.0; Biomedical Imaging Resource, Mayo Clinic, Rochester MN, USA)



Lancet Neurol 2008; 7: 299–309

EPITHET Stroke Trial

Lancet Neurol 2008; 7: 299–309

52 patients to alteplase and 49 patients to placebo

Inclusion Criteria

- Patients with acute hemispheric ischaemic stroke who presented 3–6 h after symptom onset,
- 18 years of age or older,
- NIHSS>4,
- premorbid modified Rankin score (mRS) of 2 or less.

Endpoint

- **The primary endpoint was infarct growth between baseline DWI and the day 90 T2 lesion in mismatch patients.**
- Major secondary endpoints were reperfusion, good neurological outcome, and good functional outcome.

EPITHET Stroke Trial

Lancet Neurol 2008; 7: 299–309

RESULTS

Alteplase was non-significantly associated with **lower infarct growth** and significantly associated with **increased reperfusion** in patients who had mismatch**.**

Because reperfusion was associated with improved clinical outcomes, phase III trials beyond 3 h after treatment are warranted.

	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.

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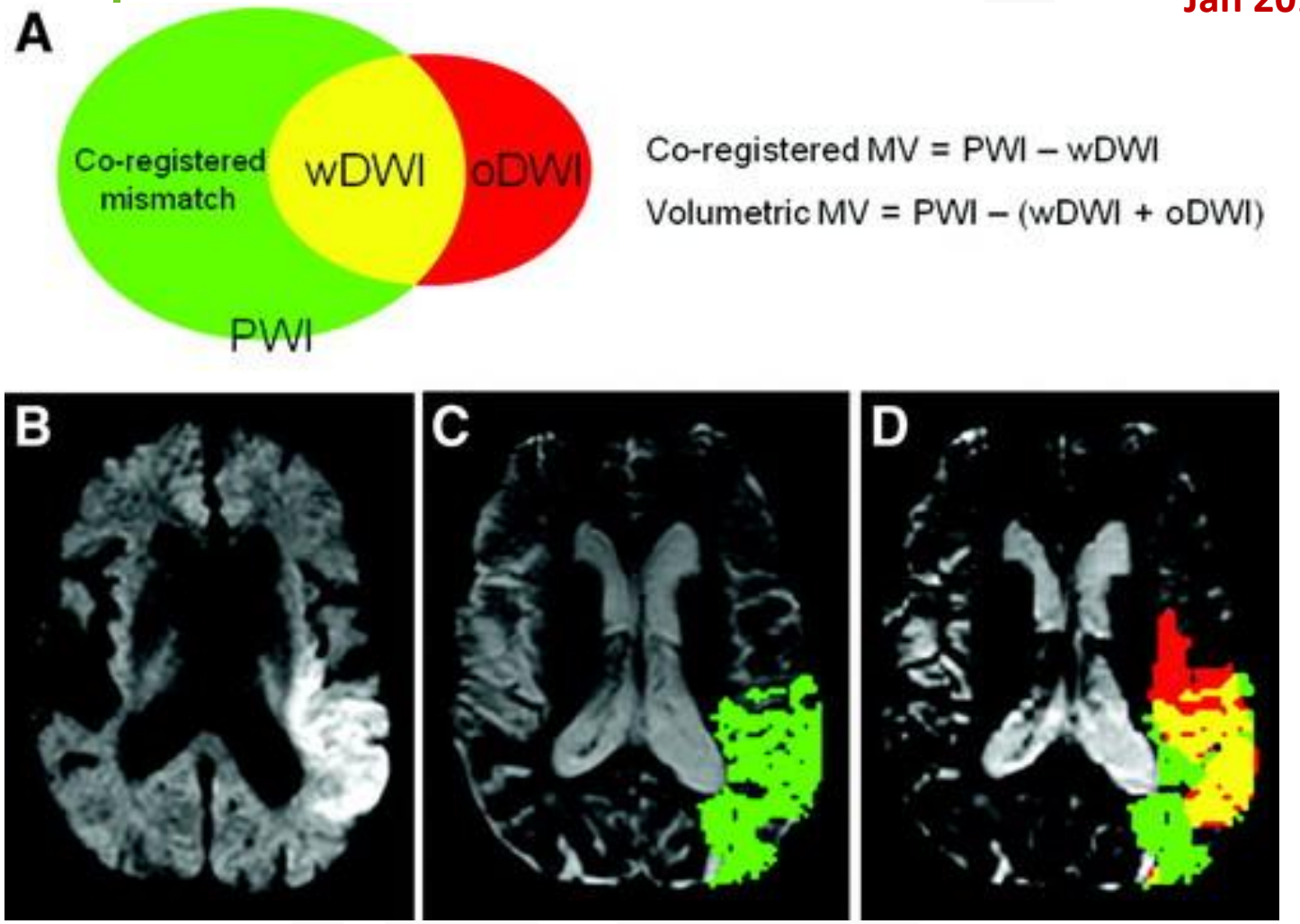
Jan 2011

Yoshinari Nagakane. Stroke. EPITHET, Volume: 42, Issue: 1, Pages: 59-64, DOI: (10.1161/STROKEAHA.110.580464)



When using coregistration techniques to determine the presence of mismatch at study entry, alteplase significantly attenuated infarct growth. This highlights the necessity for a randomized, placebo-controlled, phase III clinical trial of alteplase using penumbral selection beyond 3 hours.

ECASS4 Stroke Trial

Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection

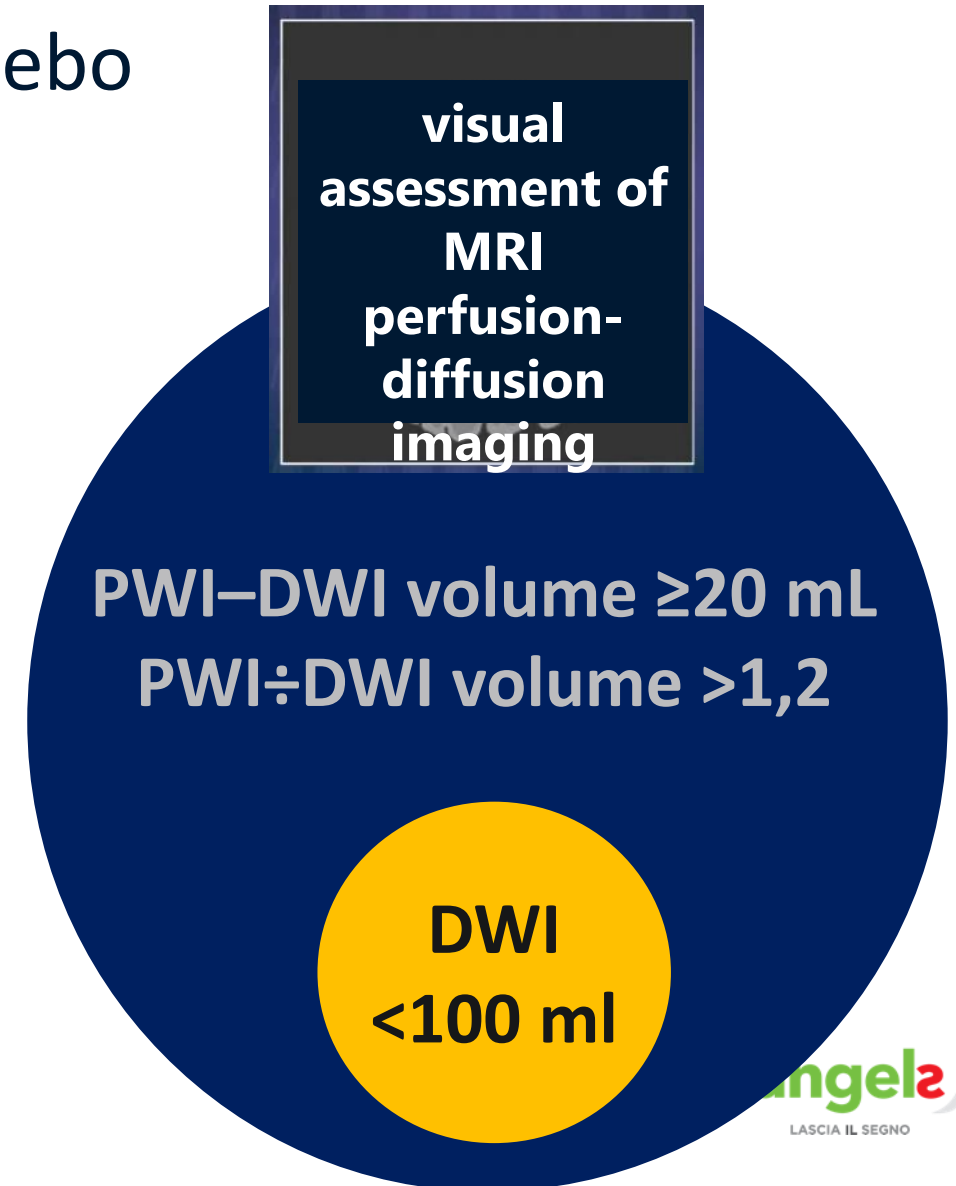
Int J Stroke 2019 Jul;14(5):483-490.

rt-PA or placebo

Ischemic stroke patients presenting within 4.5 and 9 h of stroke onset, who fulfil clinical requirements:

- National Institutes of Health Stroke Score (NIHSS) 4-26

- pre-stroke modified Rankin Scale (mRS) 0-1



ECASS4 Stroke Trial

phase 3, randomized, multi-center, double-blind, placebo-controlled study.

Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection

Int J Stroke 2019 Jul;14(5):483-490.

for slow recruitment after the enrollment of 119 (61 alteplase, 58 placebo) of 264 patients planned

Intravenous alteplase administered between 4.5 and 9 h after the onset of symptoms in patients with salvageable tissue **did not result** in a significant benefit over placebo

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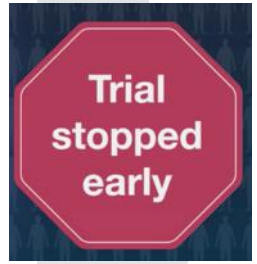
EXTEND Stroke Trial

N Engl J Med 2019; 380:1795-1803

multicenter, randomized, placebo-controlled trial involving patients with ischemic stroke who had hypoperfused but salvageable regions of brain **detected on automated perfusion imaging (CT/MRI)**

rt-Pa or placebo between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke (if within 9 hours from the midpoint of sleep)

The primary outcome was a score of 0 or 1 on the modified Rankin scale at 90 days



After 225 of the planned 310 patients had been enrolled, the trial was terminated because of **a loss of equipoise** after the publication of positive results from WAKE-UP trial

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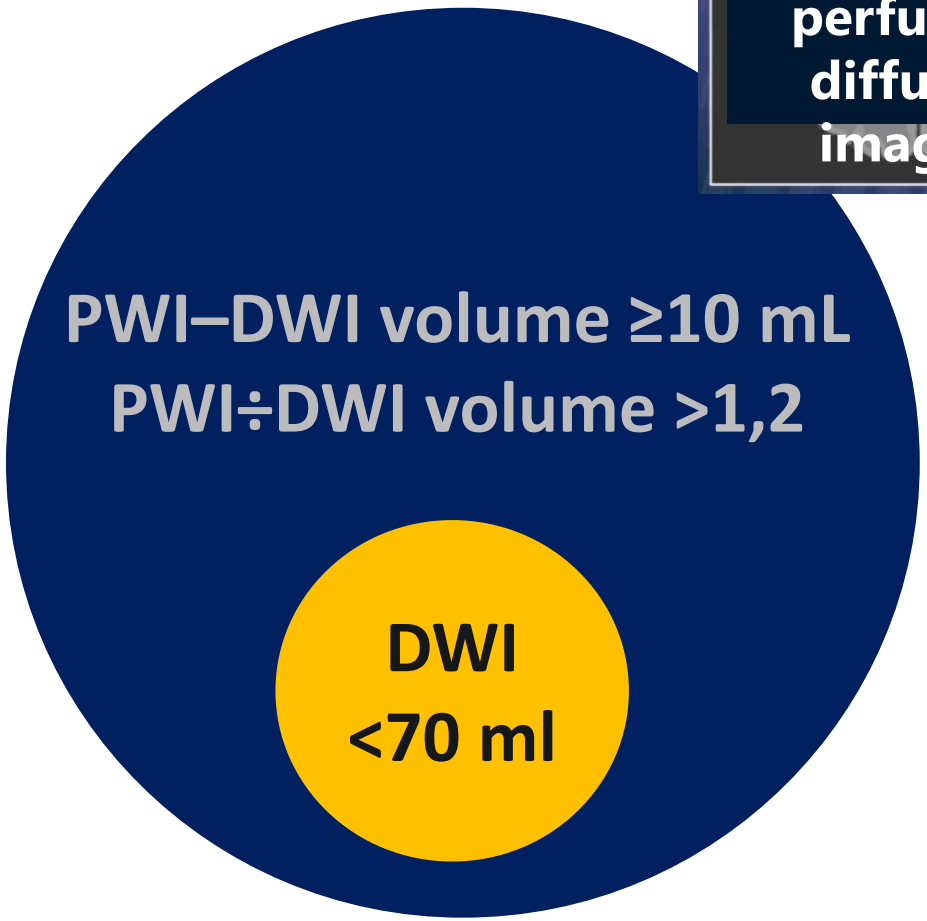
EXTEND Stroke Trial

N Engl J Med 2019; 380:1795-1803

Automated assessment of MRI perfusion-diffusion imaging

Patients eligible for inclusion

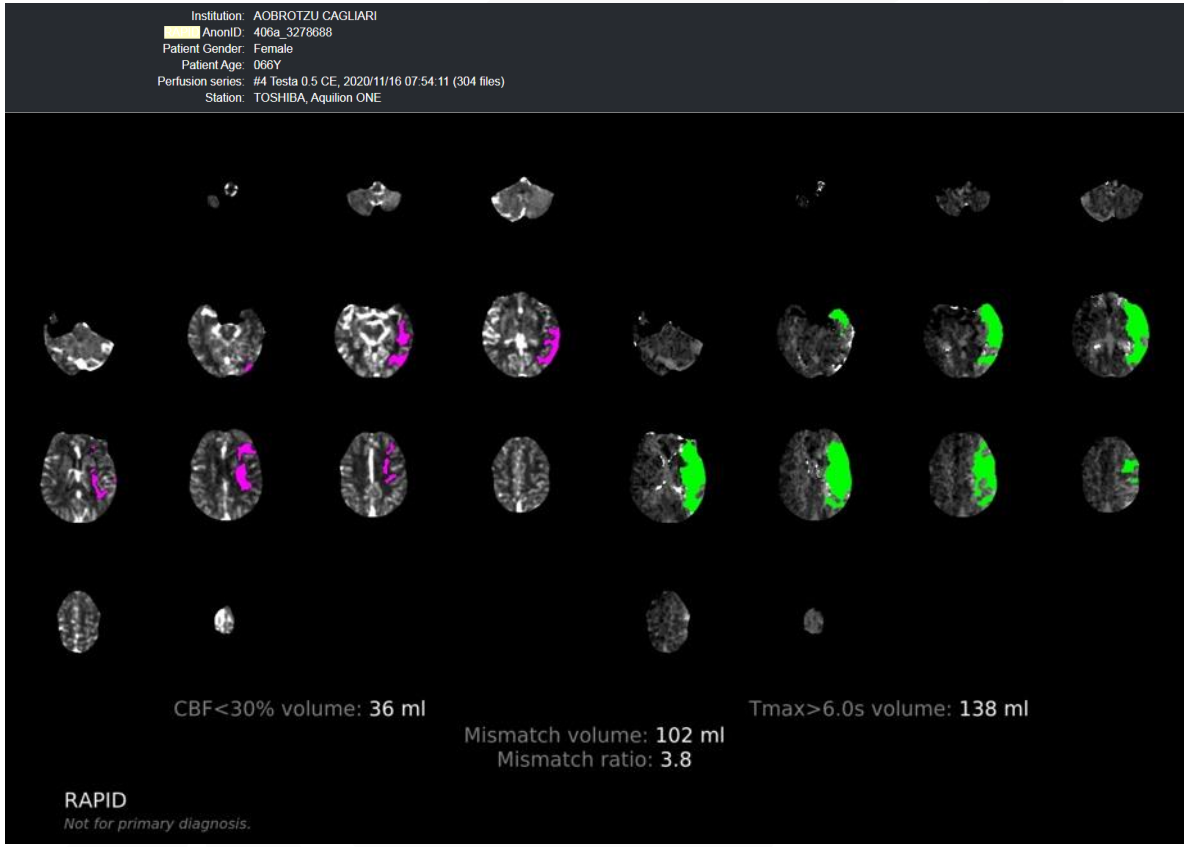
- at least 18 years of age;
- a score of <2 on the modified Rankin scale
- NIHSS 4 to 26
- hypoperfused but salvageable regions of brain detected on automated perfusion imaging.

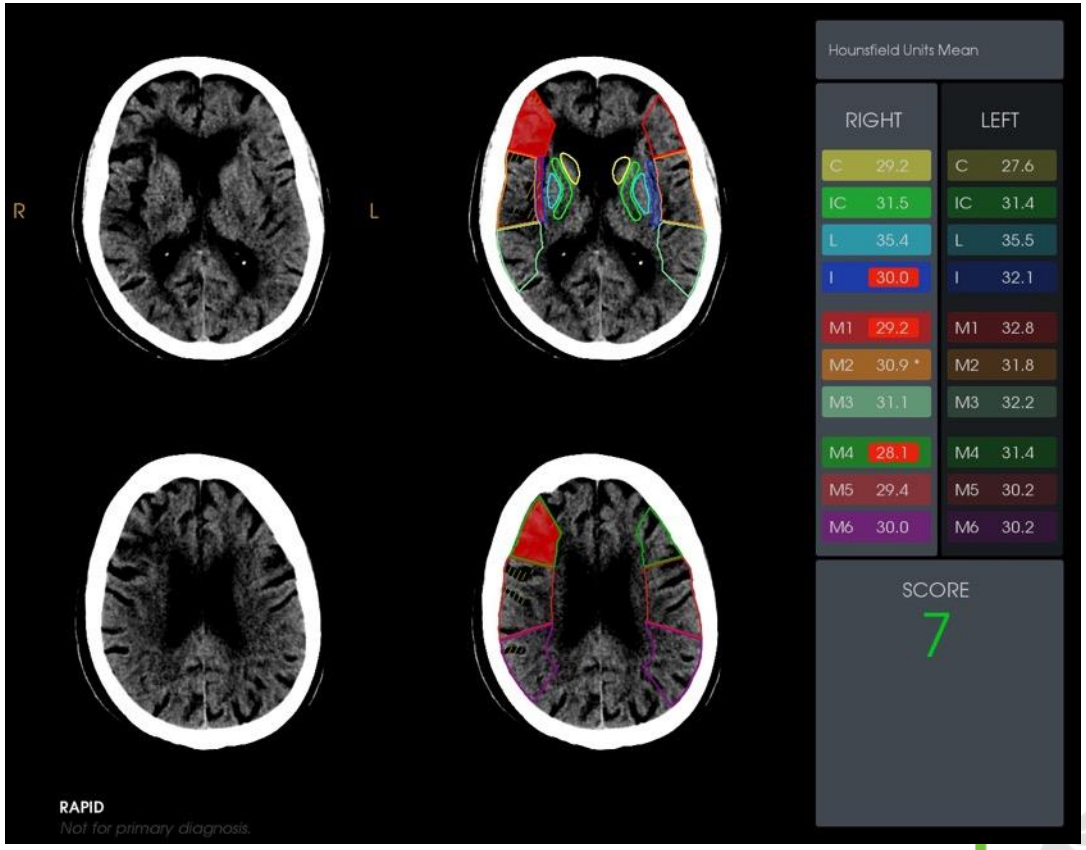


EXTEND Stroke Trial

N Engl J Med 2019; 380:1795-1803

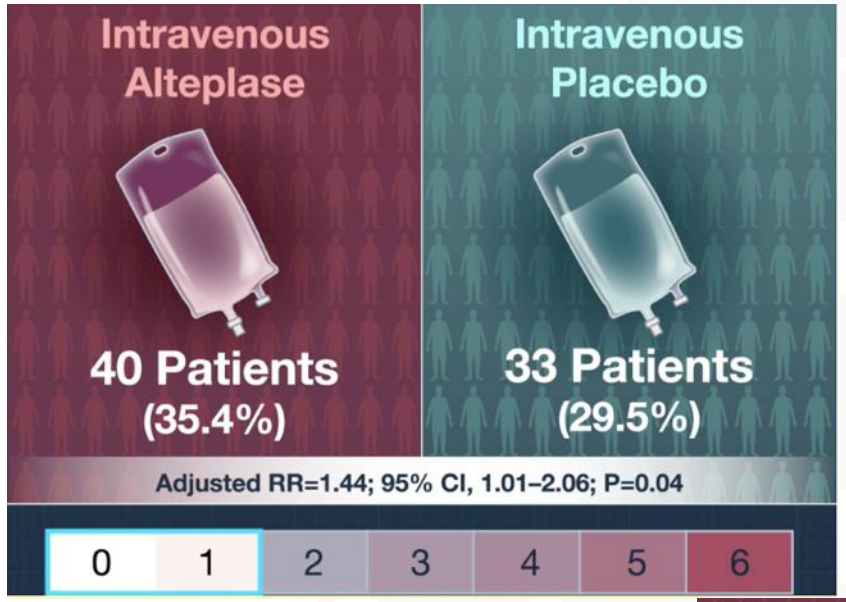
Automated assessment of MRI /CT imaging

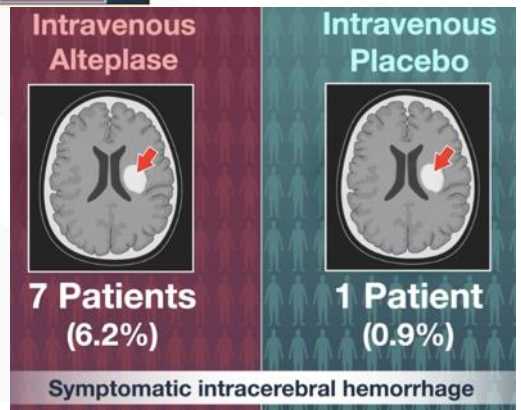


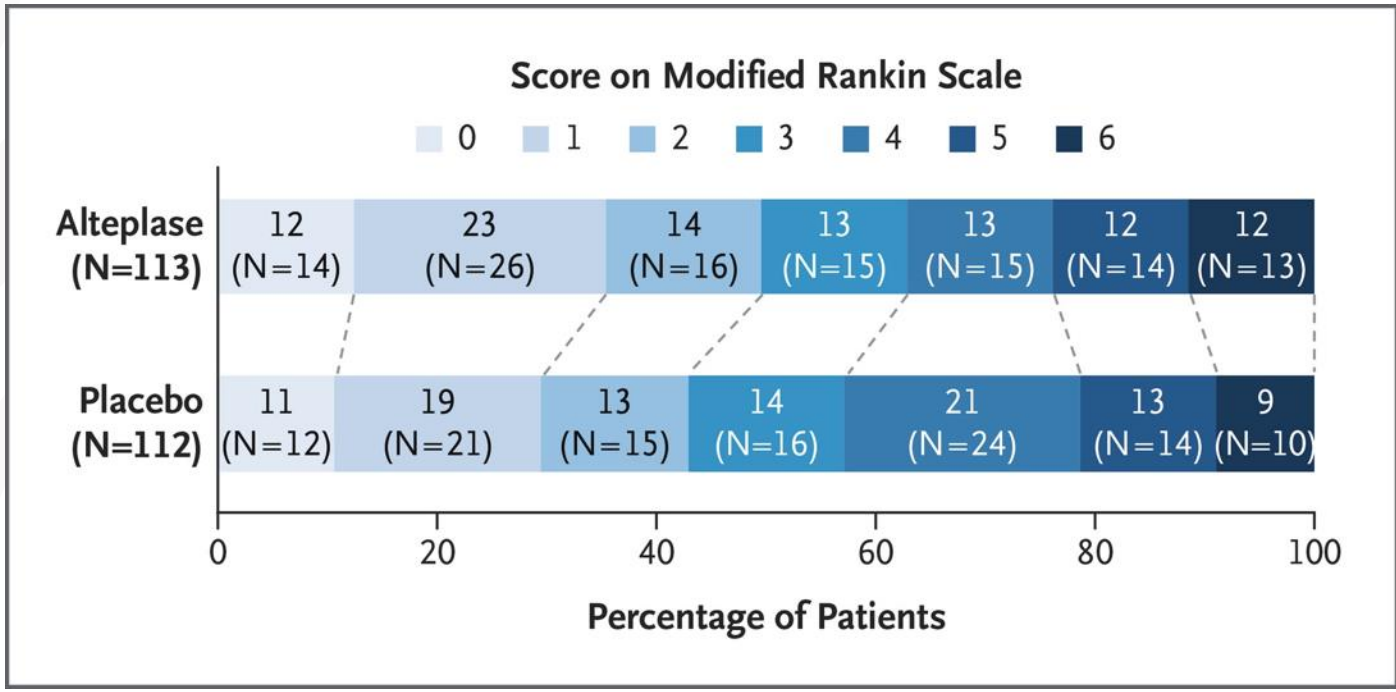


EXTEND Stroke Trial

N Engl J Med 2019; 380:1795-1803





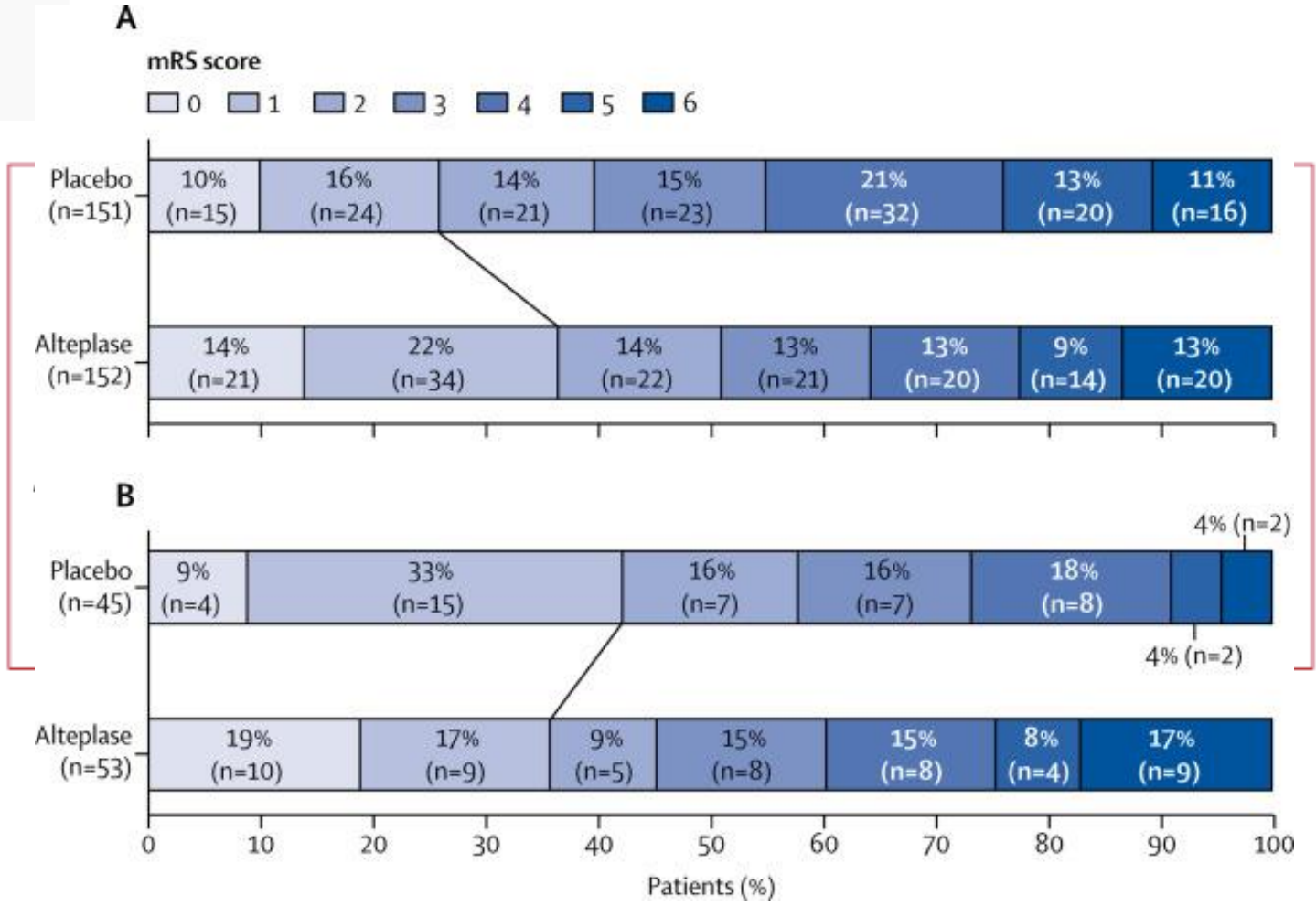


A meta-analysis of individual patient data from EXTEND, ECASS4-EXTEND and EPITHET

Lancet 2019 Jul 13;394(10193):139-147.

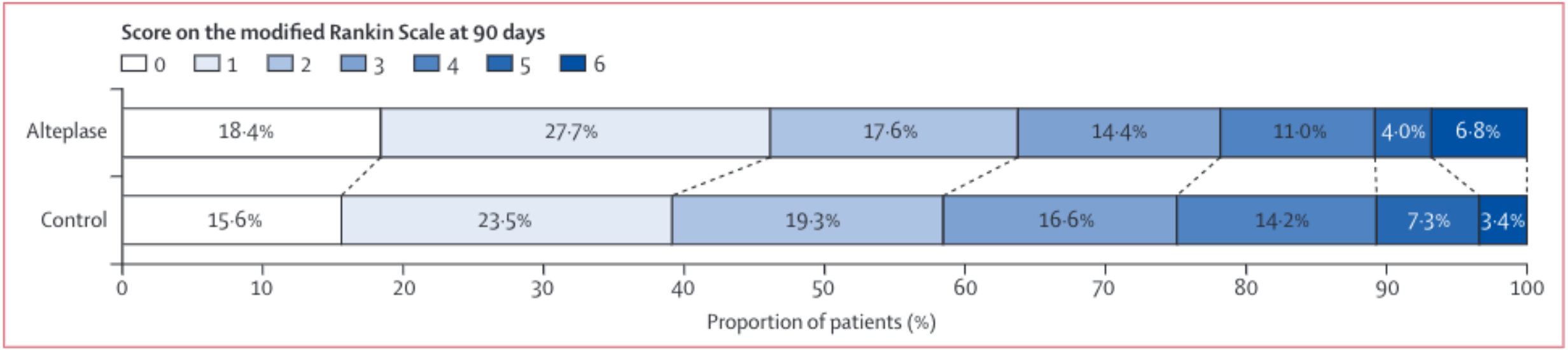
Results

Alteplase improves excellent functional outcomes (mRS 0-1) at 3 months when administered 4.5-9h or after wake-up stroke



mRS score for patients with automated perfusion mismatch (A), and patients without automated perfusion mismatch (B).

WAKE-UP, EXTEND, THAWS, and ECASS-4



In patients who have had a stroke with unknown time of onset with a DWI-FLAIR or perfusion mismatch, intravenous alteplase resulted in better functional outcome at 90 days than placebo or standard care despite an increased risk of symptomatic intracranial haemorrhage.

Although there were more deaths with alteplase than placebo, there were fewer cases of severe disability or death.

Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data

*Götz Thomalla, Florent Boutitie, Henry Ma, Masatoshi Koga, Peter Ringleb, Lee H Schwamm, Ona Wu, Martin Bendszus, Christopher F Bladin, Bruce C V Campbell, Bastian Cheng, Leonid Churilov, Martin Ebinger, Matthias Endres, Jochen B Fiebach, Mayumi Fukuda-Doi, Manabu Inoue, Timothy J Kleinig, Lawrence L Latour, Robin Lemmens, Christopher R Levi, Didier Leys, Kaori Miwa, Carlos A Molina, Keith W Muir, Norbert Nighoghossian, Mark W Parsons, Salvador Pedraza, Peter D Schellinger, Stefan Schwab, Claus Z Simonsen, Shlee S Song, Vincent Thijs, Danilo Toni, Chung Y Hsu, Nils Wahlgren, Haruko Yamamoto, Nawaf Yassi, Sohei Yoshimura, Steven Warach, Werner Hacke, Kazunori Toyoda, Geoffrey A Donnan, Stephen M Davis, Christian Gerloff, on behalf of the Evaluation of unknown Onset Stroke thrombolysis trials (EOS) investigators**

Lancet 2020; 396: 1574–84

Wake Up Stroke

Is mismatch RM PW-DWI o CT Perfusion available?

Yes

Criteri EXTEND

A PWI-DWI mismatch is used for penumbral estimation. Mismatch is defined as PWI:DWI ratio of ≥ 1.2 and an absolute difference in volume greater than 10 ml, Ischemic core lesion of less than or equal to 70 mL.

NO

Criteri WAKE-UP

DWI-FLAIR mismatch (abnormal signal on DWI and no marked signal change on FLAIR in the region of the acute stroke).

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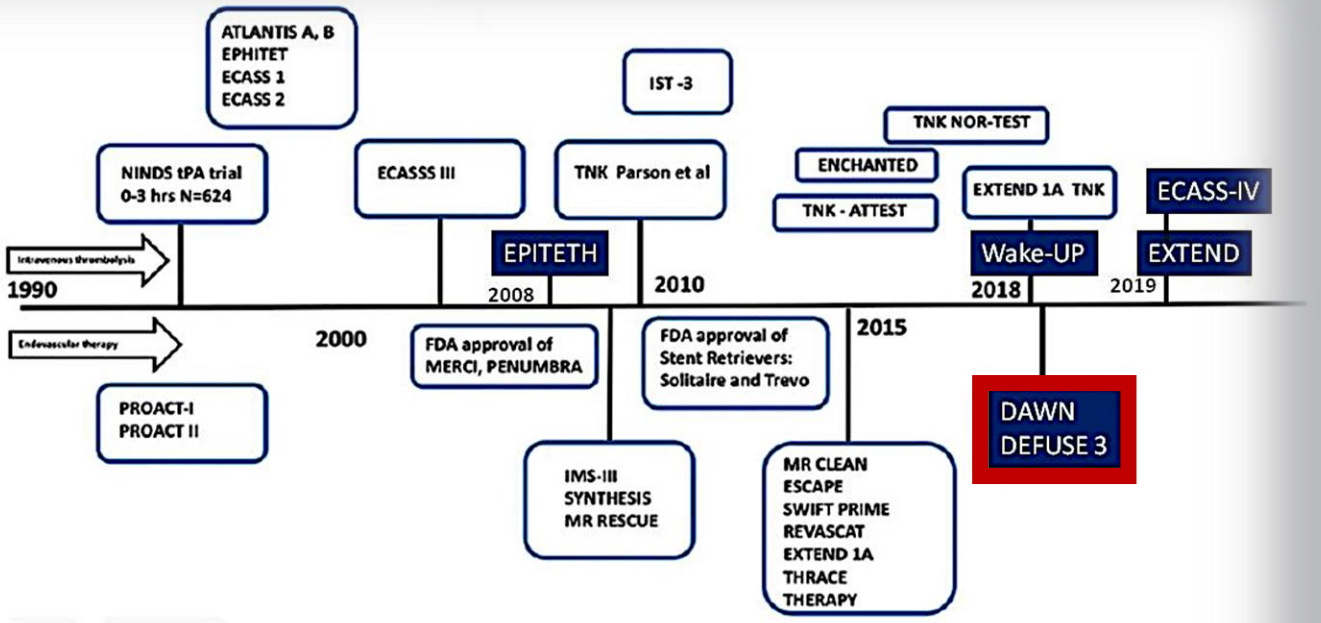
DAWN TRIAL

defuse 3



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Inclusion Criteria

Int J Stroke. 2017 Aug;12(6):641-652.

1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups:
   a. Subject has **failed IV t-PA therapy** (defined as a confirmed persistent occlusion 60 min after administration)
   b. Subject is **contraindicated for IV t-PA** administration
2. Age ≥18
3. Baseline **NIHSS ≥10**
4. Subject can be randomized between with **6 to 24 h** after time last known well
5. No significant pre-stroke disability (pre-stroke **mRS must be 0 or 1**)
6. Anticipated life expectancy of at least 6 months
7. Subject willing/able to return for protocol required follow-up visits
8. Subject or subject's legally authorized representative (LAR) has signed the study informed consent form

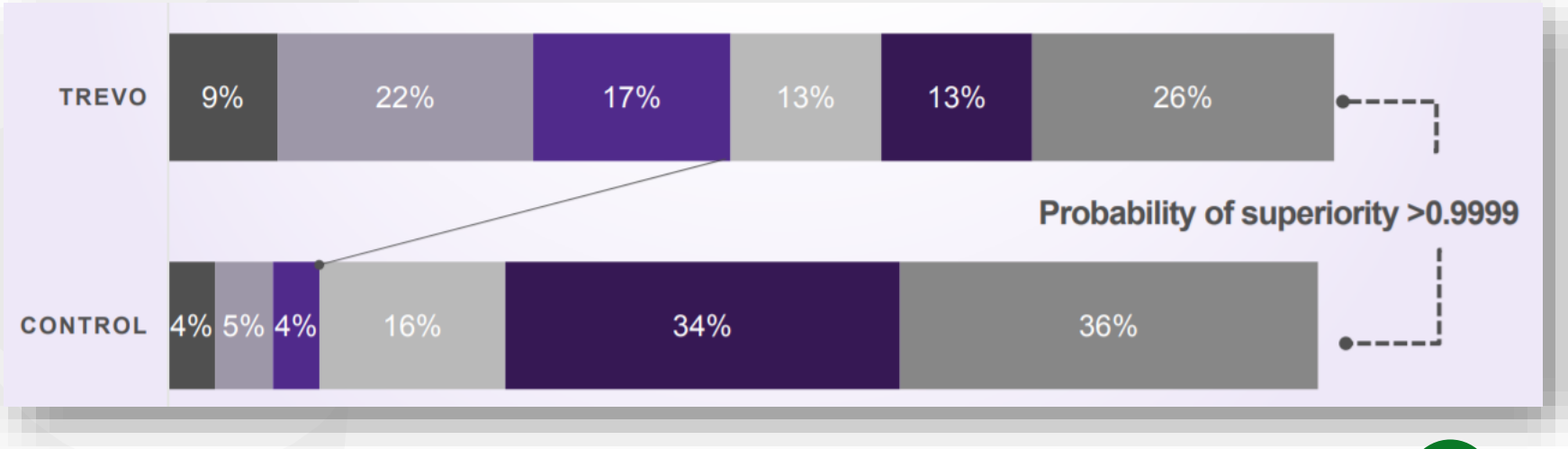
1. <1/3 MCA territory involved, as evidenced by CT or MRI
2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA
3. **Clinical imaging mismatch (CIM)** defined as one of the following on MR-DWI or CTP-rCBF maps:
   a. ≥ 80 y/o, NIHSS ≥10 + core <21 mL
   b. < 80 y/o, NIHSS ≥10 + core <31 mL
   c. < 80 y/o, NIHSS ≥20 + core <51 mL

Clinical imaging mismatch

N Engl J Med. 2018 Jan 4;378(1):11-21

Results

90 Day mRS



73% relative risk reduction of dependency in ADL's NNT for any lower disability 2.0

The treatment effect size in DAWN is the highest out of any stroke trials to date and suggests that the presence of Clinical-Core Mismatch is a critical predictor of treatment effect independent of time to presentation

	Trevo	MM	P-value
6-12h	55.1%	20.0%	<0.001
12-24h	43.1%	7.4%	<0.001

90 day Rankin 0-2

Int J Stroke. 2017 Oct;12(8):896-905.

defuse 3

1. Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke
2. Age 18–90 years
3. Baseline **NIHSS score ≥6**
4. **Endovascular treatment** can *be i*nitiated (femoral puncture) between **6 and 16 h** of stroke onset. Stroke onset is defined as the time the patient was last known to be at their neurologic baseline (wake-up strokes are eligible if they meet the above time limits)
5. **Modified Rankin Scale ≤2** prior to qualifying stroke
6. Patient/Legally authorized representative has signed the informed consent form

Inclusion Criteria

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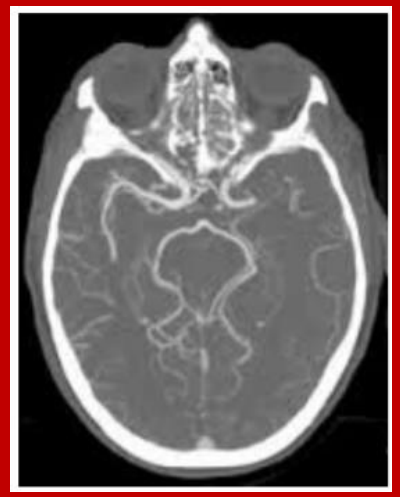
Int J Stroke. 2017 Oct;12(8):896-905.

MRA / CTA reveals

- M1 segment MCA occlusion, or
- ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)



AND

Target Mismatch Profile on CT perfusion or MRI (RAPID)

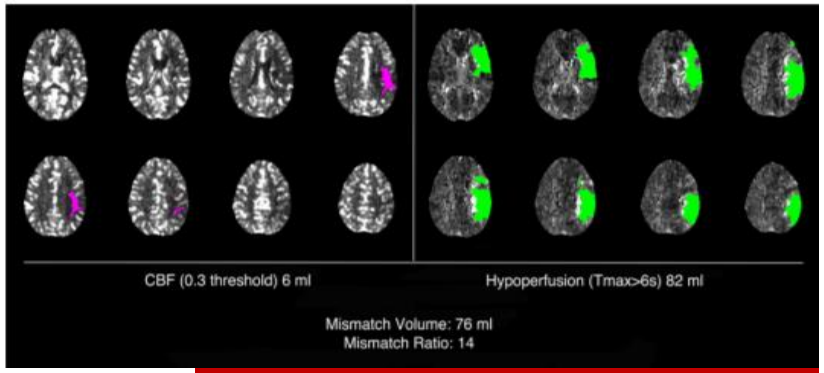
- Ischemic core volume < 70 mL

and

- Mismatch ratio > 1.8

and

- Mismatch volume ≥ 15 mL



defuse·3

Inclusion Criteria

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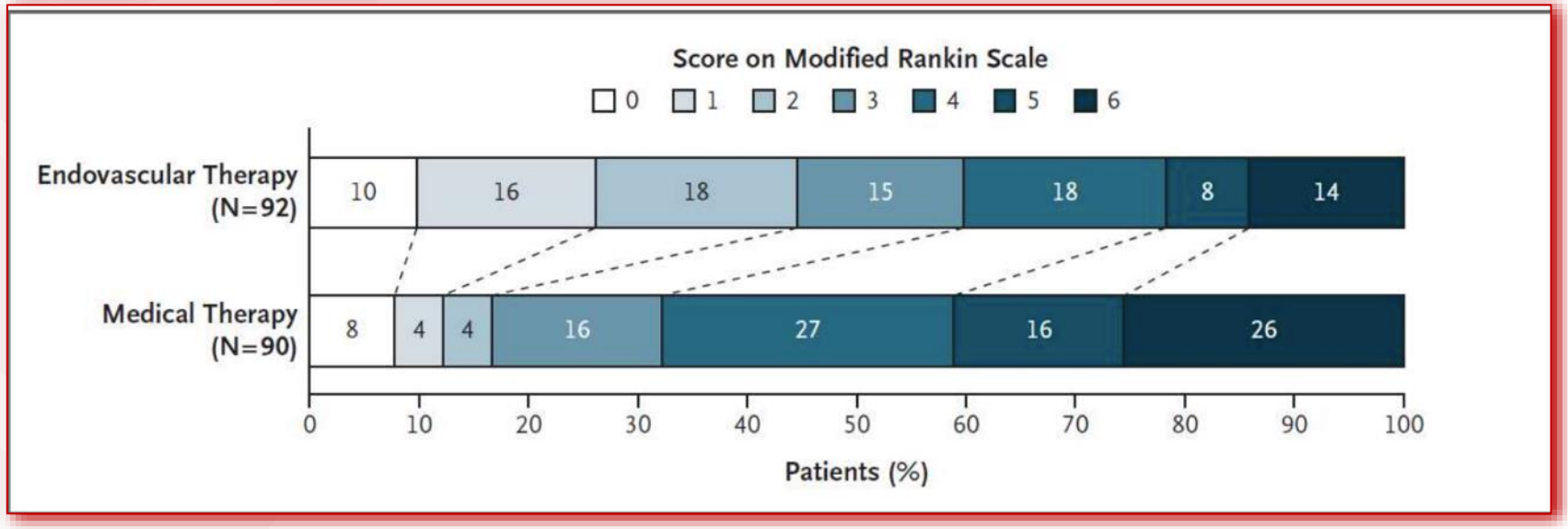
defuse 3

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

Results

Endovascular thrombectomy for ischemic stroke 6 to 16 hours after a patient was last known to be well plus standard medical therapy resulted in

better functional outcomes than standard medical therapy alone among patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion and a region of tissue that was ischemic but not yet infarcted.



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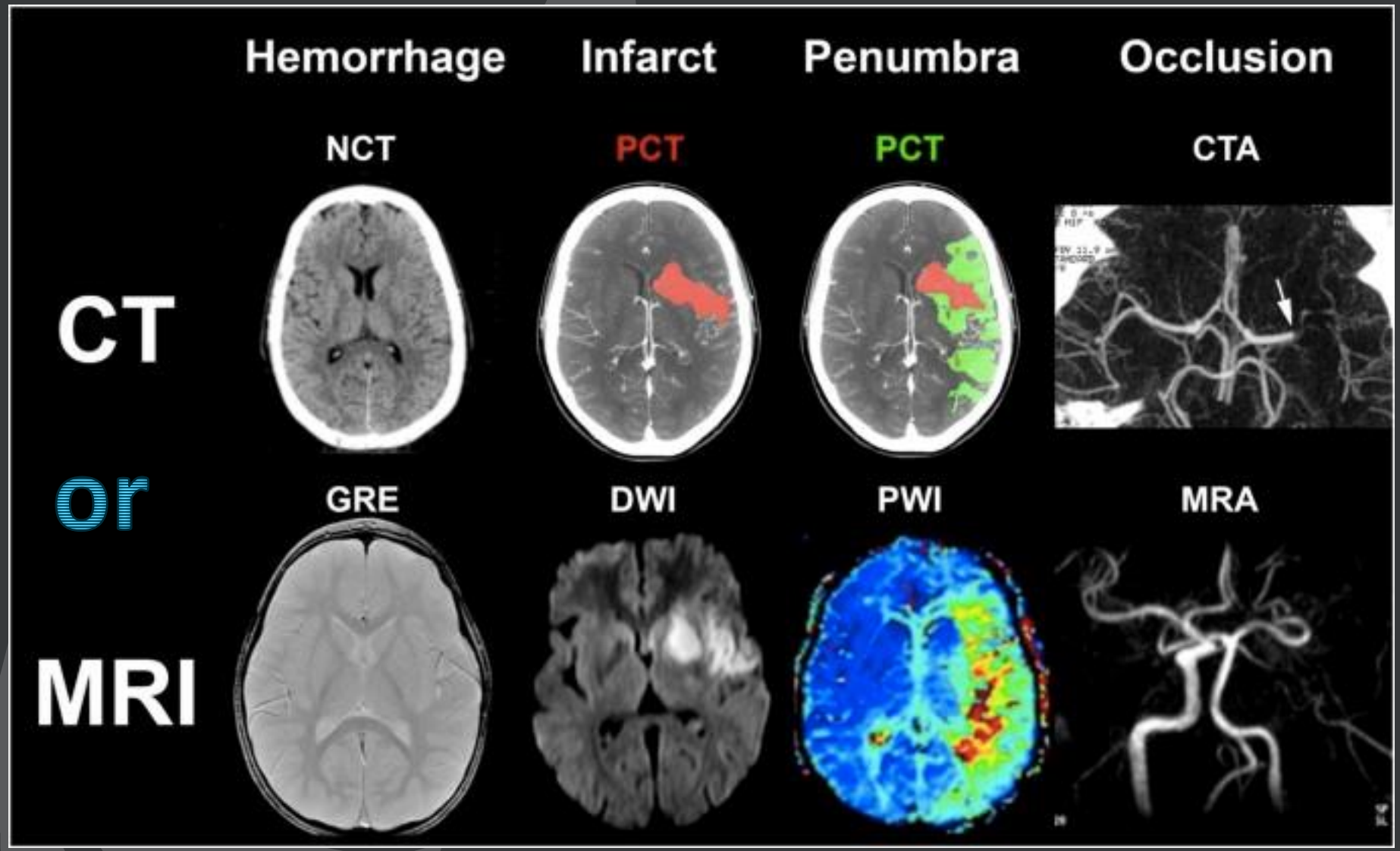
Conclusioni

La RMN, sulla base delle evidenze attuali, ricopre un ruolo determinante nella selezione dei pazienti da sottoporre a terapie riperfusive secondo le seguenti valutazioni:

- mismatch DWI-Flair per la fibrinolisi endovena nei pazienti con Ictus al Risveglio (studio Wake-UP)
- mismatch PW/DWI nei pazienti da sottoporre a fibrinolisi endovena oltre le 4.5 ore e sino alle 9 ore (Studio EXTEND)
- mismatch Gravità clinica/DWI e PW/DWI nel selezionare pazienti da sottoporre a trombectomia meccanica oltre le 6 ore (rispettivamente studio DAWN e Defuse 3)
- l'analisi automatica dell'estensione del core e del mismatch sembra offrire un vantaggio


Hemorrhage
Infarct
Penumbra
Occlusion
NCT
PCT
PCT
CTA
CT
or
MRI
GRE
DWI
PWI
MRA

RACCOMANDAZIONE PER LA RICERCA 9.32

In pazienti con ictus ischemico acuto da occlusione di grossa arteria di circolo anteriore entro 6 ore dall'esordio dei sintomi e ASPECTS <6 e core ischemico >70 ml, è raccomandata l'inclusione in RCT.

RACCOMANDAZIONE 9.33 Grado GPP

In pazienti con ictus ischemico acuto da occlusione di grossa arteria di circolo anteriore entro 6 ore dall'esordio dei sintomi e ASPECTS 3-5 o core ischemico >70 ml, qualora non sia possibile l'arruolamento in trial randomizzati, il Gruppo di lavoro suggerisce la possibilità di effettuare il trattamento endovascolare, ma la decisione dovrebbe prendere in considerazione l'età del paziente, lo stato funzionale pre-esistente e il tempo stimato per ottenere la riperfusione.

Extension of the time window for therapy is the most logical way to increase the number of patients eligible to receive rt-PA.

MRI allows the identification of ischemic Penumbra by depicting the mismatch between the hypoperfused perfusion weighted image (PWI) and the infarct core seen on the diffusion weighted image (DWI) and may be present in up to 50% of patients presenting within 24 h from stroke onset.

Ringleb P et al, Int J Stroke. 2019;14(5):483