Trombolisi per l’ictus ischemico acuto: esplorando il “grigio”

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Ospedale del Mare

28/09/2023
Napoli SURGERY

Trombolisi

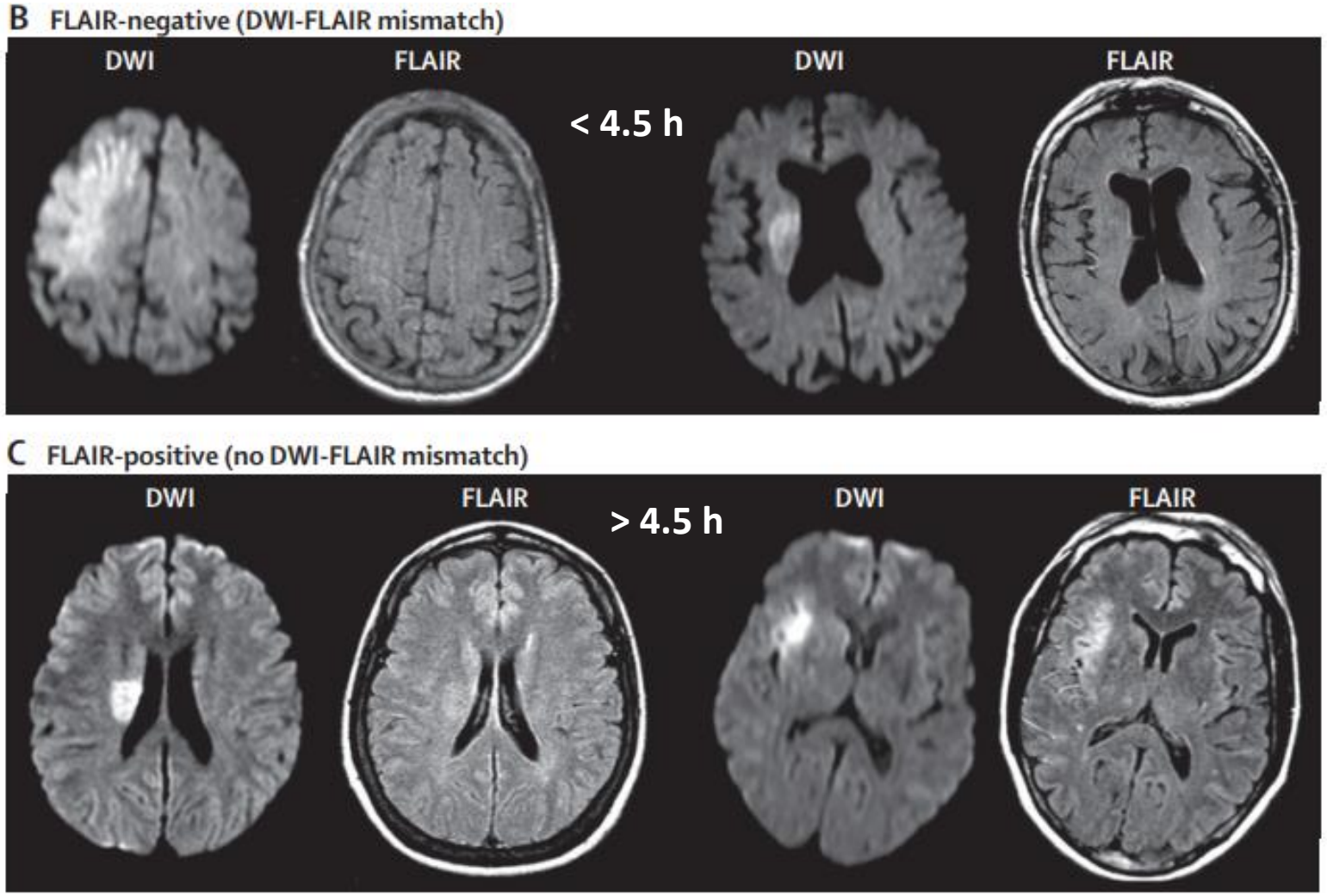
Attualmente approvato per l'ictus ischemico entro le 4.5 h senza limiti di età e di gravità clinica

Possibile il trattamento fino alle 9h in casi selezionati (ECASS IV, EXTEND, EPITHET e WAKE-UP)

Eppure la scelta se trattare o meno il paziente rappresenta ancora oggi una sfida per il clinico..

Ictus al risveglio?

- ≈15%



L1)

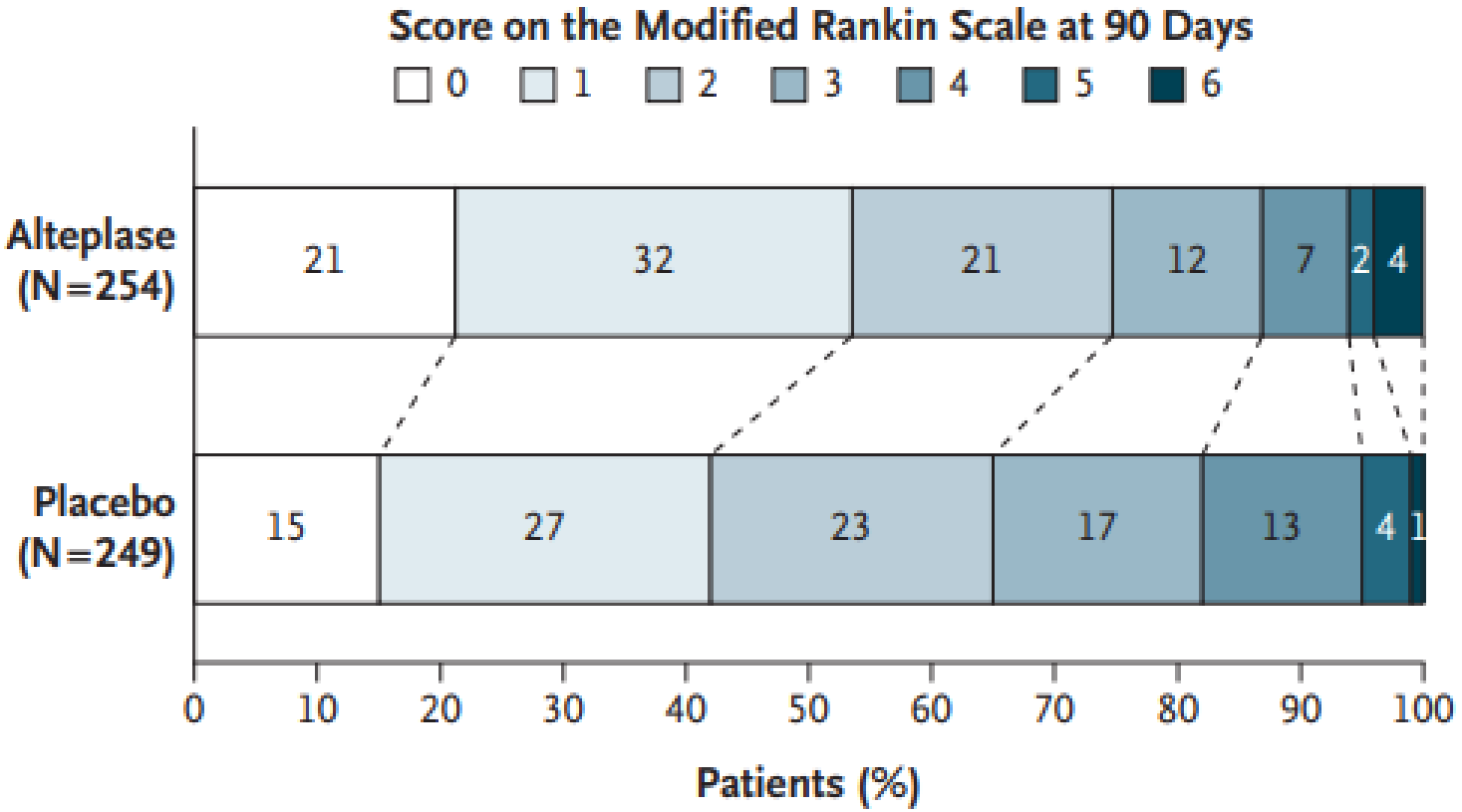
tients with
onset

er C Singer, Steven Warach,
rmann, Matthias Endres,
Serloff, for the STIR and VISTA

Lancet Neurol 2011; 10: 978–86

Wake-up stroke Trial

- ✓ Age 18-80 y
- ✓ NIHSS ≤ 25; pre Stroke mRS ≤ 1
- ✓ Last known well > 4.5 h of treatment initiation but Treatment can be start within 4.5 h of symptom recognition (ie wakening)



503 pts –
median NIHSS 6;
Median last known well to IVT time: 10 h
Arterial occlusion 34% -

Thomalla G et al, NEJM 2018

Wake up and unknown stroke onset: individual patient data meta-analysis

Published in final edited form as:

Lancet. 2020 November 14; 396(10262): 1574–1584. doi:10.1016/S0140-6736(20)32163-2.

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

Götz Thomalla, MD[1] [Prof.], Florent Boutitie, PhD[2], Henry Ma, PhD[3] [Prof.], Masatoshi Koga, MD[4], Peter Ringleb, MD[5], Lee H. Schwamm, MD[6] [Prof.], Ona Wu, PhD[7], Martin Bendszus, MD[8] [Prof.], Christopher F Bladin, MD[9] [Prof.], Bruce C.V. Campbell, PhD[10]

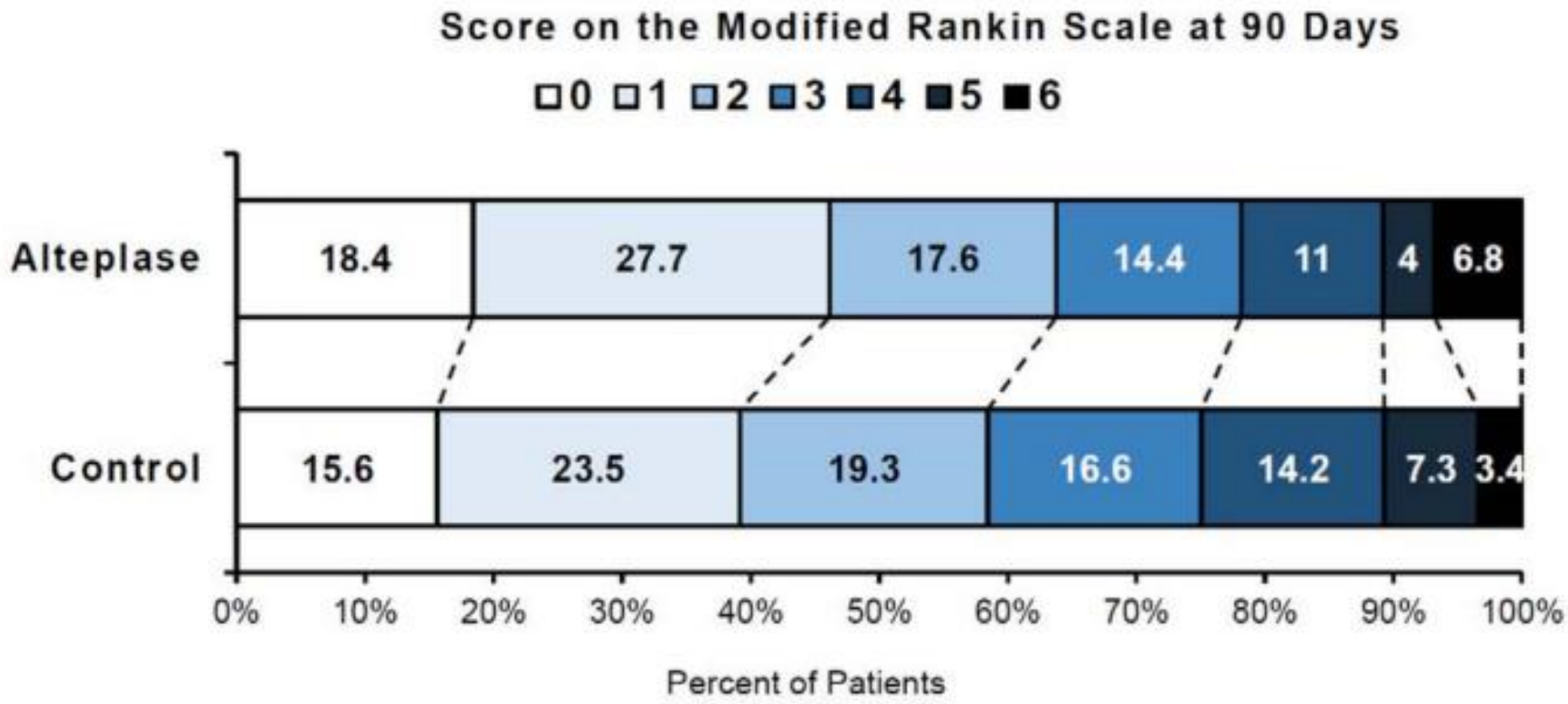
Wake-Up, THAWS, EXTEND, ECASS-4

843 patients randomized

- **Wake-up** stroke: **90%** of cases
- **Median last-known-well to alteplase time 10.6 hrs** (8.6 – 12.4)
- **Median NIHSS 7** (4-12)
- MRI: 85%
- Proximal occlusion: 25% (thrombectomy not performed)
- Mismatch:

FLAIR-DWI: 95%

Penumbral: 54%



outcome eccellente mRs 0-1 ($P = 0.01$; $I^2 = 27\%$)

mRS ≤2: adj OR 1.50 (1.06–2.12), P=0.02

Death: adj OR 2.06 (1.03–4.09), P=0.04

sICH: adj OR 5.58 (1.22–25.50), P=0.02

Thomalla et al, Lancet 2020

Cosa dicono le linee guida..

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** ↑↑

✅ TROMBOLISI se mismatch DWI/FLAIR o perfusione core/penombra negli ictus a risveglio

e nell’ictus ad esordio noto tra le 4.5 - 9h ?

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

www.thelancet.com **Published online May 22, 2019** **http://dx.doi.org/10.1016/S0140-6736(19)31053-0**

Bruce C V Ca

Outcome

Excellent
4.5-6h
6-9h
Subtotal

Good out
4.5-6h
6-9h
Subtotal

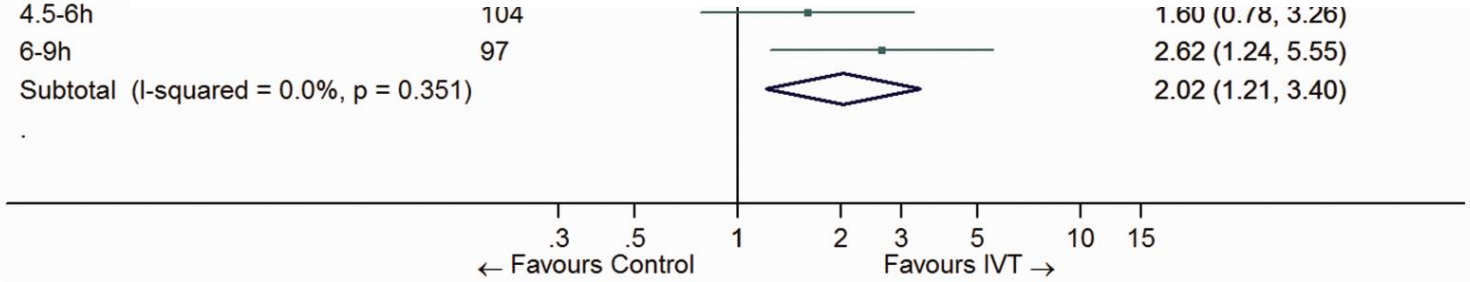
Better fu
4.5-6h
6-9h
Subtotal (I-squared = 0.0%, p = 0.351)

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** ↑↑



/I
'I
ombra
)

Cosa dicono le linee guida..

Pazienti candidati a trombectomia meccanica ma anche al trattamento con trombolisi nella finestra tra 4.5 – 9h?

Expert consensus statement:

For patients presenting **directly to a thrombectomy centre** with ischaemic stroke of 4.5-9 h duration **(known onset)** with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, the group members **could not reach a consensus** regarding whether intravenous thrombolysis should be used before mechanical thrombectomy.

For patients presenting to **a non-thrombectomy centre** with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, 6 of 9 group members **suggest intravenous thrombolysis before mechanical thrombectomy.**

European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischemic stroke and anterior circulation large vessel occlusion

Evidence-based recommendation

For patients directly admitted to a thrombectomy-capable center for an acute ischemic stroke (≤4.5 hours of symptom onset) with anterior circulation large vessel occlusion and who are eligible for both treatments, we recommend intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone.

Both treatments should be performed as early as possible after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis, and intravenous thrombolysis should not delay mechanical thrombectomy.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Strong** ↑↑

1)DIRECT-MT
2)DEVT
3)SKIP
4) MR CLEAN NO IV
5) SWIFT-DIRECT
6) DIRECT-SAFE

2331 pts

Turc G, *et al*. *J NeuroInterv Surg* 2022;**14**:209–227. doi:10.1136/neurintsurg-2021-018589

MINOR STROKE

Definizione non univoca

Ictus ischemico associato a sintomi clinici con punteggio NIHSS $\leq$ 5

Criteri d'inclusione differenti nei singoli trials

Stroke
Volume 41, Issue 4, 1 April 2010; Pages 661-666
https://doi.org/10.1161/STROKEAHA.109.572883

American Heart Association.

ORIGINAL CONTRIBUTIONS

What Is a Minor Stroke?

Urs Fischer, MD, MSc, Adrian Baumgartner, MS, Marcel Arnold, MD, Krassen Ne

ORIGINAL CONTRIBUTIONS; BRIEF REPORTS

Ninety-Day Outcome Rates of a Prospective Cohort of Consecutive Patients With Mild Ischemic Stroke

Pooja Khatri, MD, MSc, Mark R. Conaway, PhD, Karen C. Johnston, MD, MSc, and for the

MINOR STROKE

NIHSS ≤5

JAMA | Original Investigation

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits
The PRISMS Randomized Clinical Trial

Pooja Khatri, MD, MSc; Dawn O. Kleindorfer, MD; Thomas Devlin, MD; Robert N. Sawyer Jr, MD; Matthew Starr, MD; Jennifer Mejilla, DO; Joseph Broderick, MD; Anjan Chatterjee, MD; Edward C. Jauch, MD, MS; Steven R. Levine, MD; Jose G. Romano, MD; Jeffrey L. Saver, MD; Achala Vagal, MD, MS; Barbara Purdon, PhD; Jenny Devenport, PhD; Andrey Pavlov, PhD; Sharon D. Yeatts, PhD; for the PRISMS Investigators

PRISMS Trial:

«a deficit that, if unchanged, would prevent the patient from performing basic activities of daily living (ie, bathing, ambulating, toileting, hygiene, and eating) or returning to work»

Disabilitanti:

-afasia grave-moderata

-emianopsia

-deficit motorio/sensitivo con compromissione di un arto

Non disabilitanti:

-deficit faciale isolato

-lieve emisindrome sensori-motoria o atassica

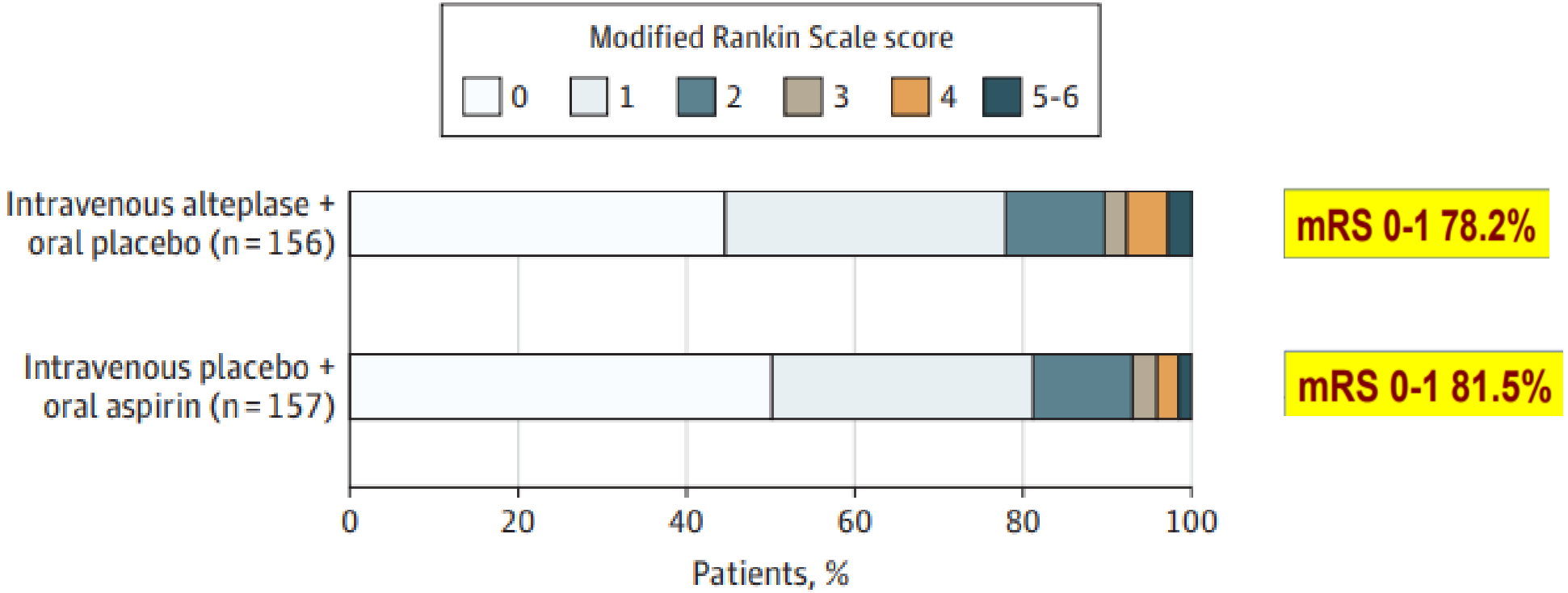
-lieve afasia

-lieve deficit della mano (soprattutto se non dominante)

PRISMS Trial

- 313 pazienti randomizzati (su 948 pianificati)
- Alteplase ev vs. aspirina ad alte dosi
- NIHSS <u>≤5</u> (media 2)
- Interrotto precocemente

Miglior outcome a 90 giorni nel sottogruppo trattato con aspirina (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%).



mRS 0-1 78.2%

mRS 0-1 81.5%

JAMA July 10, 2018 Volume 320, Number 2

Eventi avversi

	No. (%)		
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)	Risk Difference, % (95% CI)
Primary Adverse Event Assessment			
Symptomatic intracranial hemorrhage within 36 h	5 (3.2)	0	3.3 (0.8 to 7.4)
Secondary Adverse Event Assessments			
Symptomatic intracranial hemorrhage within 36 h, SITS-MOST definition[a]	2 (1.3)	0	1.3 (−1.2 to 4.6)
Any radiologic intracranial hemorrhage within 36 h by central reader	11 (7.1)	5 (3.3)	3.9 (−1.2 to 9.5)
By radiological subtype[b]			
Hemorrhagic infarction type 1	2	3	
Hemorrhagic infarction type 2	2	1	
Parenchymal hematoma type 1	1	0	
Parenchymal hematoma type 2	4	0	
Remote parenchymal hematoma type 1	2	0	
Intraventricular hemorrhage	2[c]	0	
Subarachnoid hemorrhage	3[c]	1	
Mortality within 90 d	1 (0.6)	0	
Stroke-related and neurologic deaths within 90 d	0	0	
Patients with serious adverse events[d]	40 (26.0)	20 (13.1)	12.9 (4.1 to 21.7)[e]
Patients with any adverse events	119 (77.3)	104 (68.0)	

JAMA July 10, 2018 Volume 320, Number 2

(risk difference, 3.3%; 95% CI, 0.8%-7.4%).

Cosa dicono le linee guida..

PICO:

In pazienti adulti con ictus ischemico acuto entro 4.5 ore dall'esordio dei sintomi in presenza di deficit lieve (NIHSS ≤ 5) o in rapido miglioramento ma ancora rilevabile al momento di iniziare il trattamento, la trombolisi con r-TPA e.v., confrontata con aspirina, migliora l'esito clinico?

Raccomandazione 4

Grado Forte a Favore

Evidenza (1+)

Elevata ⊕⊕⊕⊕

LINEE GUIDA ITALIANE SPREAD (ISA-AII)

EUROPEAN STROKE JOURNAL

troke Organisation (ESO)
n intravenous thrombolysis
chaemic stroke

European Stroke Journal
2021, Vol. 6(1) I–LXII

DOI: 10.1177/2396987321989865
journals.sagepub.com/home/eso
SAGE

ndation

nor, disabling ischaemic stroke of less than 4.5 hours' duration,

is thrombolysis with alteplase.

rate ⊕⊕⊕

Metanalisi su 9 trials randomizzati (6756 pazienti)

NINDS, ECASS I-II-III, ATLANTIS A-B, EPITHET, IST-3

per i minor stroke disabilitanti

Cosa dicono le linee guida..

Evidence-based Recommendation

For patients with acute, minor non-disabling ischaemic stroke of less than 4.5 hours' duration, we suggest no intravenous thrombolysis with alteplase. For patients with minor stroke and large-vessel occlusion, please refer to the section 9.3.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Weak** ↓?

✕ Trombolisi NO per i minor stroke non disabilitanti

ARAMIS

Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke

JAMA | Original Investigation

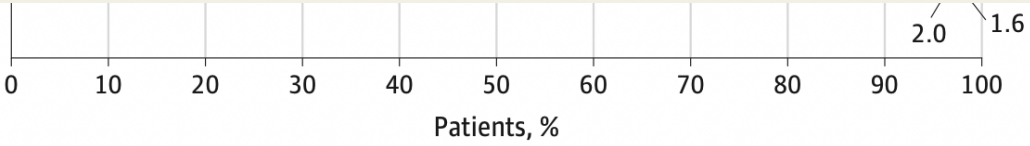
Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke

The ARAMIS Randomized Clinical Trial

Hui-Sheng Chen, MD; Yu Cui, PhD; Zhong-He Zhou, MD; Hong Zhang, BSM; Li-Xia Wang, BSM; Wei-Zhong Wang, BSM; Li-Ying Shen, BSM; Li-Yan Guo, MM; Er-Qiang Wang, MM; Rui-Xian Wang, MM; Jing Han, MM; Yu-Ling Dong, BSM; Jing Li, BSM; Yong-Zhong Lin, MD; Qing-Cheng Yang, BSM; Li Zhang, BSM; Jing-Yu Li, MM; Jin Wang, BSM; Lei Xia, BSM; Guang-Bin Ma, BSM; Jiang Lu, BSM; Chang-Hao Jiang, BSM; Shu-Man Huang, BSM; Li-Shu Wan, MM; Xiang-Yu Piao, MD; Zhuo Li, MM; Yan-Song Li, MM; Kui-Hua Yang, BSM; Duo-Lao Wang, PhD; Thanh N. Nguyen, MD; for the ARAMIS Investigators

Safety outcomes (safety population)						
Symptomatic intracerebral hemorrhage[i]	1/371 (0.3)	3/352 (0.9)	Risk difference[c]	−0.6% (−1.7% to 0.5%)	.30	−2.4% (−12.1% to 7.3%)	.63
			Risk ratio[c]	0.32 (0.03 to 3.02)	.32	0.31 (0.03 to 2.99)	.36
Any bleeding events[j]	6/371 (1.6)	19/352 (5.4)	Risk difference[c]	−3.8% (−6.5% to −1.1%)	.006	−3.6% (−6.4% to −0.7%)	.01
			Risk ratio[c]	0.30 (0.12 to 0.74)	.009	0.31 (0.12 to 0.76)	.01

in ciascun item



- DAPT per 14 giorni vs Alteplase

Non inferiorità della DAPT vs fibrinolisi a 90 giorni

Prospettive future..

TEMPO -2

NIH U.S. National Library of Medicine

ClinicalTrials.gov

A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO-2)

- PROBE Trial in 50 centri nel mondo
- NIHSS <5 entro le 12h
- Aprile 2015 – Dicembre 2024
- Tenecteplase vs. antiaggregante standard

TAKE HOME MESSAGES:

- **La trombolisi** intravenosa è **indicata nei pazienti con ictus a risveglio** (entro le 9h) che rispettino i criteri d'inclusione alle neuroimmagini
- Nei pazienti con ictus **ad esordio noto tra le 4.5 – 9 h è consigliato trattare con trombolisi,** soprattutto in caso di assenza di un grosso vaso.
- L'utilizzo delle neuroimmagini avanzate rappresenta un elemento essenziale e imprescindibile nel trattamento dei pazienti in finestra estesa e nell'evoluzione in favore di una medicina sempre più «personalizzata»
- Nei **minor stroke 'disabilitanti' la trombolisi resta il trattamento di scelta**
- Nei **minor stroke** con deficit lievi (**'non disabilitanti') l'antiaggregante** rappresenta la scelta più efficace e sicura

doi:10.1093/brain/awt201 Brain 2013: 136; 3528–3553 | 3528

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

The emergence of acute thrombolysis and the quiet art of patient selection

Joyce S. Balami,[1] Gina Hadley,[2] Brad A. Sutherland,[2] Hasneen Karbalai[3] and Alastair M. Buchan[2,3,4]

GRAZIE PER L'ATTENZIONE!

*"Patient selection is both science and art. The **science** arises from **meta-analysis** of the predictive value of quantitative metrics in determining response to therapy. The **art** arises from the **gradual accumulation of clinical experience** that reassures the clinician that **they are treating the patient not just because they can, but because they expect to see a real benefit**"*