SOCIETÀ MEDICA
DI SANTA MARIA NUOVA

X EDIZIONE

Giornate Mediche di Santa Maria Nuova 2018

L'Ospedale dei Fiorentini

Il trattamento trombolitico sistemico dell'ictus. Una realtà in espansione

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Ictus cerebrale

PRIMA causa di disabilità permanente nell'anziano (terza causa di disabilità a livello mondiale, nel 35% dei pazienti residua una disabilità grave)

SECONDA causa di morte e demenza

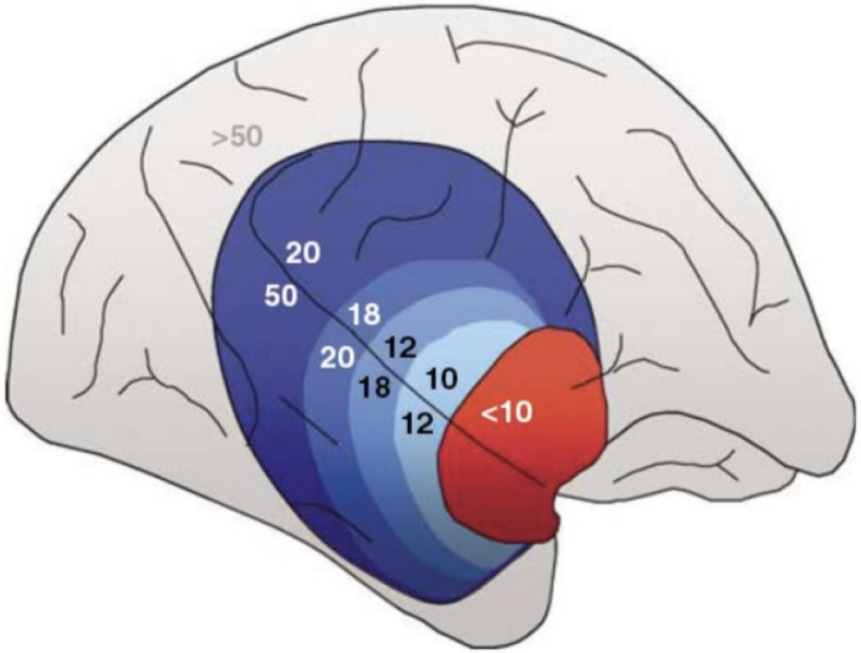
INCIDENZA IN ITALIA : negli ultimi 20aa si è passati da 180.000 a 120.000 casi/anno.

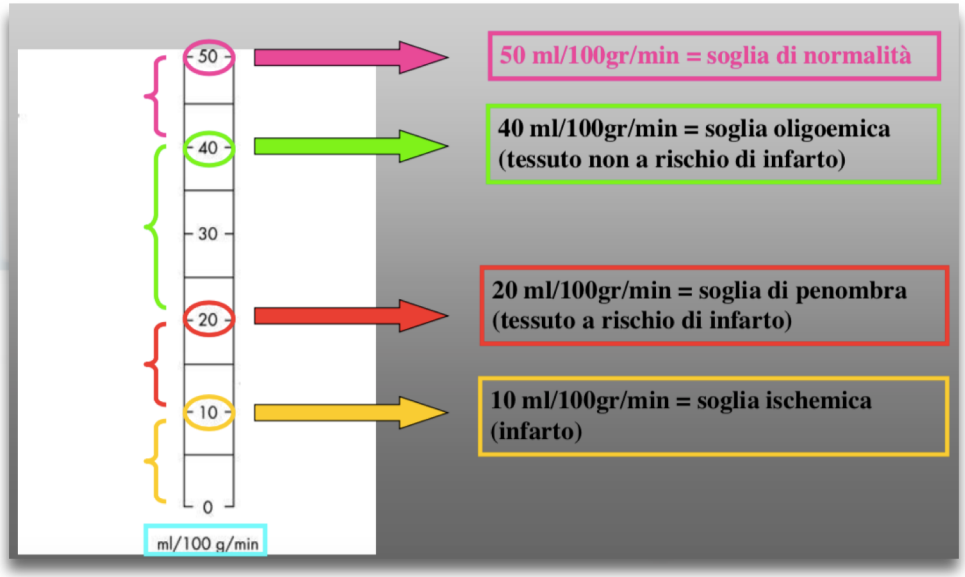
INCIDENZA DI ICTUS IN TOSCANA : 10.000/anno (80% ischemici)

Grosso impatto socio sanitario

COSTI DIRETTI stimati di circa 280 milioni di euro ogni anno (circa 30mila euro l'anno per ogni singolo disabile)

Penombra ischemica





Le dimensioni della penombra ischemica dipendono

- Efficienza dei circoli collaterali di compenso
- Severità e estensione dell'ischemia
- Durata dell'ischemia

Strategie di riperfusione

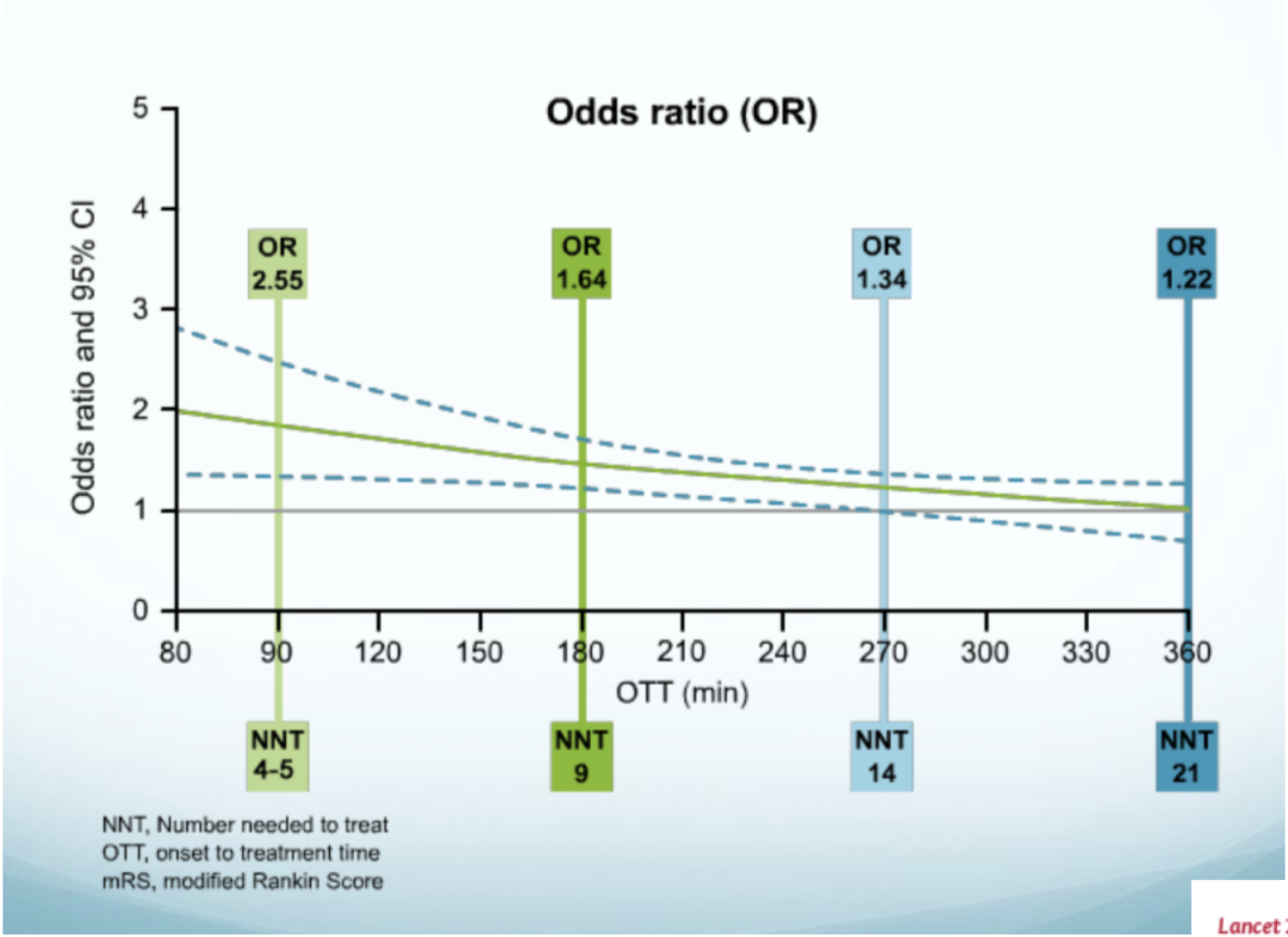
Raccomandazione 9.1 **Forte a favore** **Grado A**

Il trattamento con r-tPA e.v. (0,9 mg/kg, dose massima 90 mg, il 10% della dose in bolo, il rimanente in infusione di 60 minuti) è raccomandato entro 4.5 ore dall'esordio di un ictus ischemico senza limiti superiori di età e di gravità.
È comunque indicato che il trattamento sia effettuato il più precocemente possibile.

Raccomandazione 9.12 **Forte a favore** **Grado B**

Le tecniche di trombectomia meccanica sono raccomandate entro 6 ore dall'esordio dei sintomi in pazienti con occlusione di carotide interna intra-cranica, arteria cerebrale media tratti M1-M2, arteria cerebrale anteriore tratto A1, che non rispondono o che non possono essere sottoposti alla trombolisi e.v.

mRankin 0-1



Lancet 2014; 384: 1929–35

Time to Treatment With Intravenous Tissue Plasminogen Activator and Outcome From Acute Ischemic Stroke

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Importance Randomized clinical trials suggest the benefit of intravenous tissue-type plasminogen activator (tPA) in acute ischemic stroke is time dependent. However, modest sample sizes have limited characterization of the extent to which onset to treatment (OTT) time influences outcome; and the generalizability of findings to clinical practice is uncertain.

Objective To evaluate the degree to which OTT time is associated with outcome among patients with acute ischemic stroke treated with intraveneous tPA.

Design, Setting, and Patients Data were analyzed from 58 353 patients with acute ischemic stroke treated with tPA within 4.5 hours of symptom onset in 1395 hospitals participating in the Get With The Guidelines-Stroke Program, April 2003 to March 2012.

Main Outcomes and Measures Relationship between OTT time and in-hospital mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination.

Results Among the 58 353 tPA-treated patients, median age was 72 years, 50.3% were women, median OTT time was 144 minutes (interquartile range, 115-170), 9.3% (5404) had OTT time of 0 to 90 minutes, 77.2% (45 029) had OTT time of 91 to 180

INTRAVENOUS (IV) TISSUE-TYPE PLASminogen activator (tPA) is a treatment of proven benefit for select pa-

Each 15-minute reduction in the time to initiation of tPA treatment was associated with an increase in the odds of

- walking independently at discharge **(4 percent)**
- being discharged to home rather than an institution **(3 percent)**
- decrease in the odds of death before discharge **(4 percent)**
- decrease symptomatic hemorrhagic transformation of infarction **(4 percent)**

peutic benefit of tPA is greatest when given very early after ischemic stroke

to accelerate hospital presentation and thrombolytic treatment in patients with stroke.

JAMA. 2013;309(23):2480-2488 www.jama.com

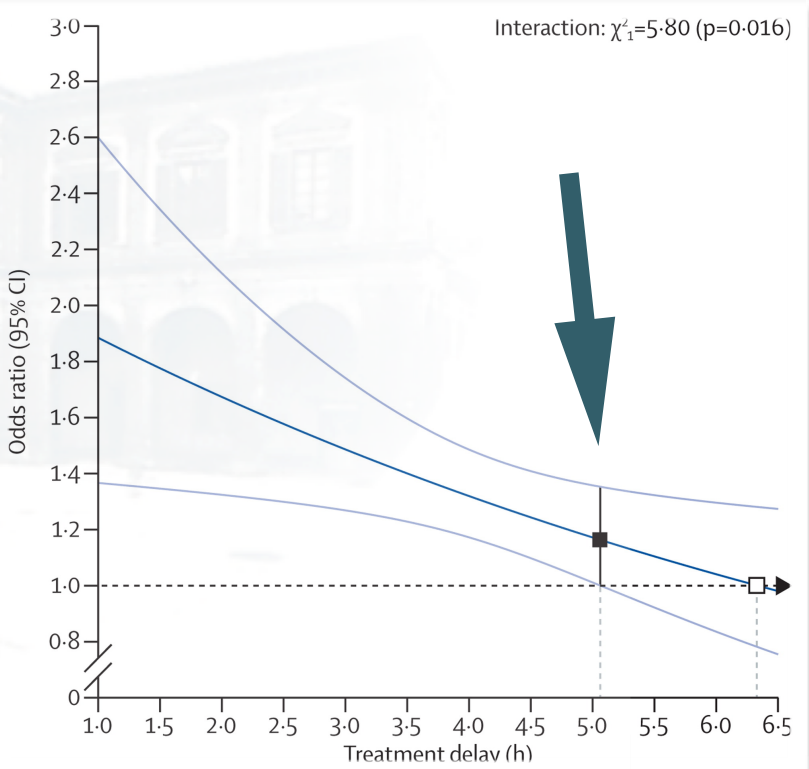
Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials

	NINDS A	NINDS B	ECASS I	ECASS II	ATLANTIS A	ATLANTIS B	ECASS III	EPITHET	IST-3	TOTAL
Number randomised	291	333	620	800	142	613	821	101	3035	6756
Treatment delay (hours)	2·0 (0·6)	2·0 (0·6)	4·4 (1·1)	4·3 (1·1)	4·3 (1·1)	4·4 (0·8)	4·0 (0·4)	4·9 (0·8)	4·2 (1·2)	4·0 (1·2)
≤3·0	290 (>99%)	333 (100%)	87 (14%)	158 (20%)	22 (15%)	39 (6%)	..	..	620 (20%)	1549 (23%)
>3·0≤4·5	1 (<1%)	..	233 (38%)	265 (33%)	53 (37%)	249 (41%)	788 (96%)	31 (31%)	1148 (38%)	2768 (41%)
>4·5	..	..	295 (48%)	370 (46%)	67 (47%)	321 (52%)	6 (1%)	69 (68%)	1266 (42%)	2394 (35%)
Missing	..	..	5 (1%)	7 (1%)	..	4 (1%)	27 (3%)	1 (1%)	1 (<1%)	45 (1%)
Age (years)	66 (11)	68 (12)	65 (12)	66 (11)	66 (13)	66 (11)	65 (12)	72 (13)	77 (12)	71 (13)
≤80	279 (96%)	289 (87%)	615 (>99%)	792 (99%)	142 (100%)	608 (>99%)	805 (98%)	76 (75%)	1418 (47%)	5024 (74%)
>80	12 (4%)	44 (13%)	5 (1%)	8 (1%)	..	3 (<1%)	15 (2%)	25 (25%)	1617 (53%)	1729 (26%)
Missing	..	..	..	..	..	2 (<1%)	1 (<1%)	..	..	3 (<1%)
Stroke severity (NIHSS)	14 (7)	15 (7)	12 (6)	12 (6)	13 (7)	11 (6)	10 (5)	13 (6)	12 (7)	12 (7)
0–4	16 (5%)	13 (4%)	34 (5%)	47 (6%)	10 (7%)	47 (8%)	98 (12%)	1 (1%)	400 (13%)	666 (10%)
5–10	78 (27%)	98 (29%)	189 (30%)	339 (42%)	57 (40%)	279 (46%)	389 (47%)	40 (40%)	1064 (35%)	2533 (37%)
11–15	68 (23%)	63 (19%)	183 (30%)	232 (29%)	28 (20%)	128 (21%)	163 (20%)	22 (22%)	601 (20%)	1488 (22%)
16–21	76 (26%)	78 (23%)	146 (24%)	113 (14%)	25 (18%)	106 (17%)	142 (17%)	29 (29%)	618 (20%)	1333 (20%)
≥22	45 (15%)	74 (22%)	28 (5%)	43 (5%)	20 (14%)	33 (5%)	18 (2%)	9 (9%)	352 (12%)	622 (9%)
Missing	8 (3%)	7 (2%)	40 (6%)	26 (3%)	2 (1%)	20 (3%)	11 (1%)	..	*	114 (2%)
Female	120 (41%)	142 (43%)	231 (37%)	331 (41%)	45 (32%)	250 (41%)	325 (40%)	43 (43%)	1570 (52%)	3057 (45%)
History of hypertension	188 (65%)	220 (66%)	258 (42%)	412 (52%)	87 (61%)	364 (59%)	514 (63%)	71 (70%)	1954 (64%)	4068 (60%)
History of stroke	49 (17%)	34 (10%)	83 (13%)	158 (20%)	31 (22%)	89 (15%)	89 (11%)	11 (11%)	699 (23%)	1243 (18%)
History of diabetes mellitus	64 (22%)	67 (20%)	81 (13%)	169 (21%)	27 (19%)	130 (21%)	129 (16%)	23 (23%)	388 (13%)	1078 (16%)
History of atrial fibrillation	55 (19%)	60 (18%)	113 (18%)	188 (24%)	37 (26%)	97 (16%)	108 (13%)	42 (42%)	914 (30%)	1614 (24%)
Aspirin use	78 (27%)	93 (28%)	87 (14%)	196 (25%)	59 (42%)	211 (34%)	201 (24%)	30 (30%)	1306 (43%)	2261 (33%)
Weight (kg)	78 (17)	78 (19)	74 (12)	75 (14)	80 (20)	79 (18)	78 (15)	75 (19)	72 (15)	75 (16)
Systolic blood pressure (mmHg)	154 (21)	152 (21)	154 (23)	152 (21)	152 (24)	152 (21)	153 (21)	148 (19)	155 (24)	154 (22)
Diastolic blood pressure (mmHg)	85 (13)	85 (14)	87 (13)	84 (13)	81 (14)	82 (14)	84 (14)	78 (13)	82 (15)	83 (14)

Categorical data presented as n (%), continuous data presented as mean (SD). NINDS=National Institute of Neurological Disorders and Stroke; ECASS=European Cooperative Acute Stroke Study; ATLANTIS=Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; EPITHET=Echoplanar Imaging Thrombolytic Evaluation Trial; IST=International Stroke Trial. *In IST-3, 244 patients had their baseline NIHSS score predicted from other measurements recorded at their baseline assessment. Ignoring these patients, the numbers of IST-3 patients in each category of baseline NIHSS score above would be 385, 972, 531, 559 and 344 respectively.

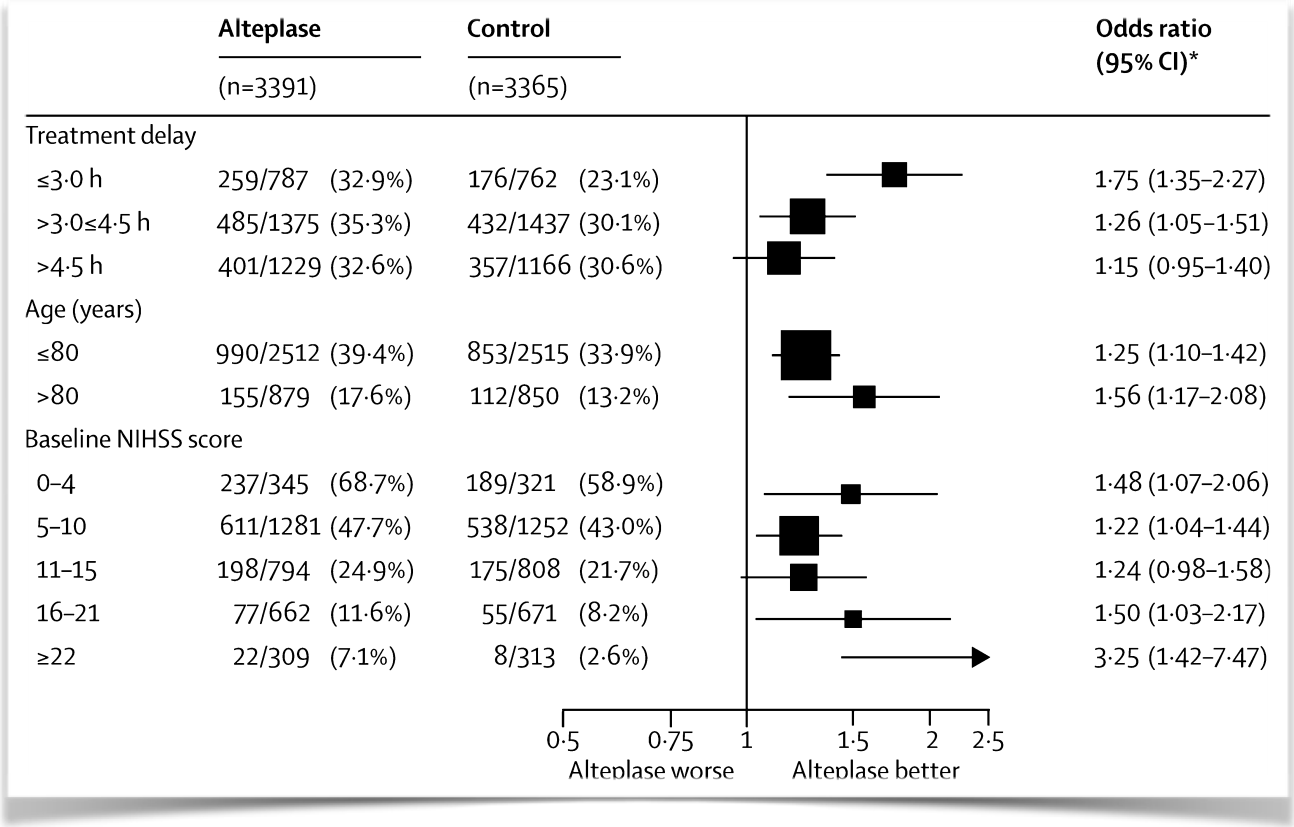
Table 1: **Baseline characteristics of patients in participating trials**

For treatment within **3 hours** of stroke onset, alteplase led to a good outcome for 33 percent, versus 23 percent for control (odds ratio [OR] 1.75, 95% CI 1.35-2.27).



Lancet 2014; 384: 1929–35

Senza limiti superiori di età e gravità



	Alteplase (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤3·0 h	259/787 (32·9%)	176/762 (23·1%)	1·75 (1·35–2·27)
>3·0≤4·5 h	485/1375 (35·3%)	432/1437 (30·1%)	1·26 (1·05–1·51)
>4·5 h	401/1229 (32·6%)	357/1166 (30·6%)	1·15 (0·95–1·40)
Age (years)			
≤80	990/2512 (39·4%)	853/2515 (33·9%)	1·25 (1·10–1·42)
>80	155/879 (17·6%)	112/850 (13·2%)	1·56 (1·17–2·08)
Baseline NIHSS score			
0–4	237/345 (68·7%)	189/321 (58·9%)	1·48 (1·07–2·06)
5–10	611/1281 (47·7%)	538/1252 (43·0%)	1·22 (1·04–1·44)
11–15	198/794 (24·9%)	175/808 (21·7%)	1·24 (0·98–1·58)
16–21	77/662 (11·6%)	55/671 (8·2%)	1·50 (1·03–2·17)
≥22	22/309 (7·1%)	8/313 (2·6%)	3·25 (1·42–7·47)

0·5 0·75 1 1·5 2 2·5

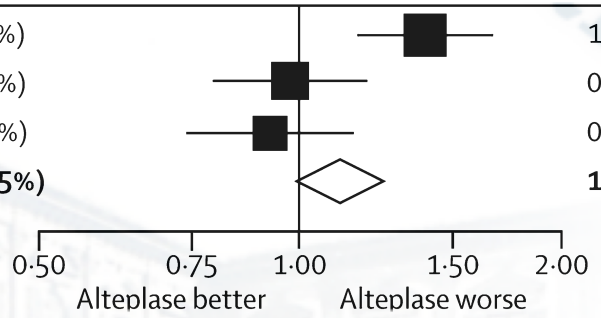
Alteplase worse Alteplase better

EVOLUZIONE DEI CRITERI DI INCLUSIONE (raccomandazioni basate sui criteri NINDS 1996. Criteri iniziali mutuati dalla letteratura di area cardiologica e da altre pubblicazioni di scienza di base)

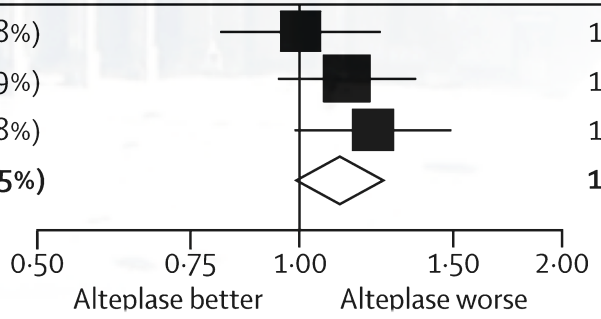
Lancet 2014; 384: 1929–35

Mortalità

	Alteplase (n=3391)	Control (n=3365)	Hazard ratio (95% CI)*
Days 1–7†	282 (8·3%)	204 (6·1%)	1·39 (1·16–1·67)
Days 8–30	178 (5·2%)	188 (5·6%)	0·97 (0·79–1·20)
Days 31–90	148 (4·4%)	164 (4·9%)	0·92 (0·74–1·15)
Total 90-day mortality	**608 (17·9%)**	**556 (16·5%)**	**1·11 (0·99–1·25)**
Test for varying log HR with increasing duration of follow-up (p<0·0001)			

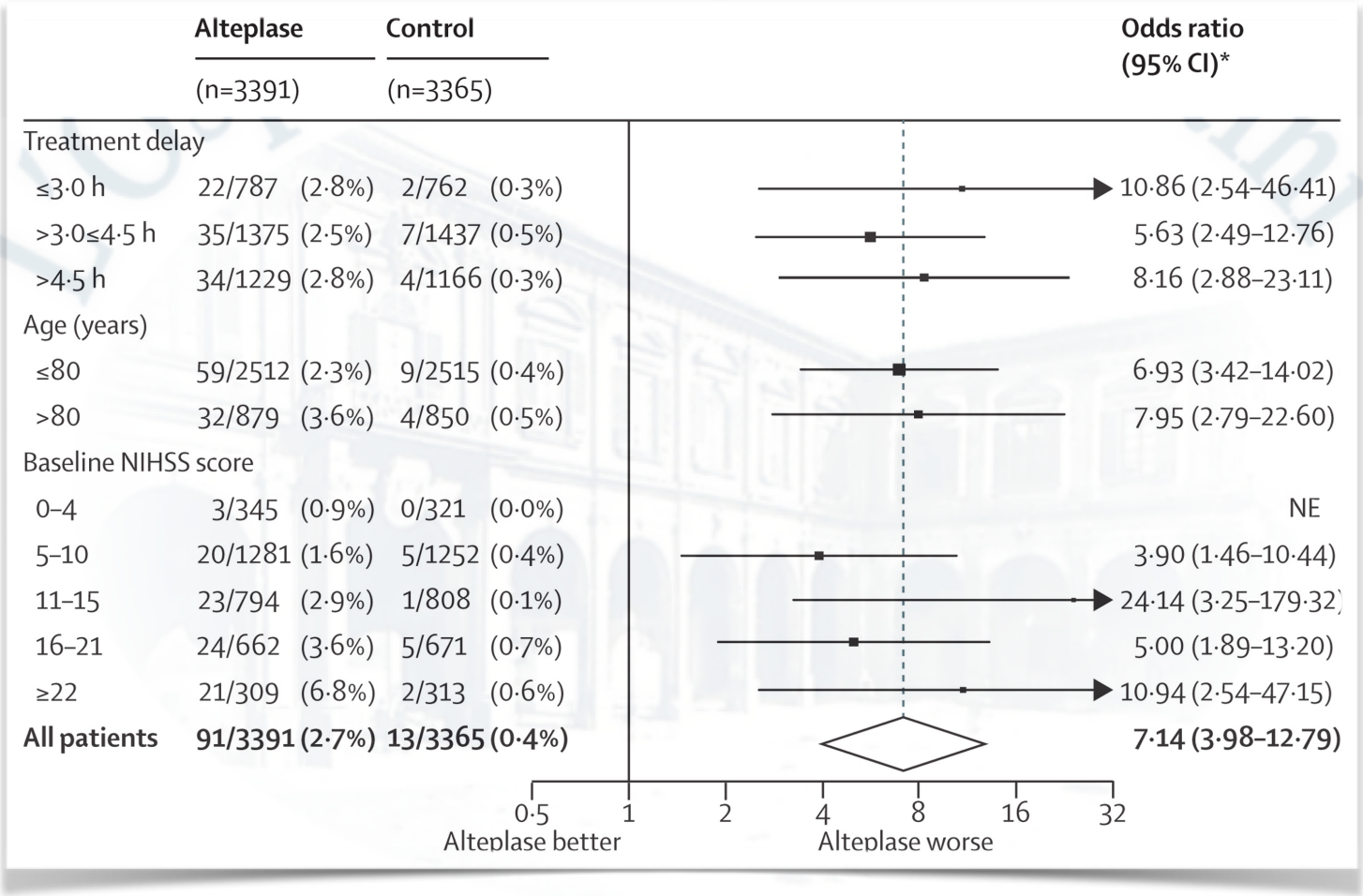


	Alteplase (n=3391)	Control (n=3365)	Hazard ratio (95% CI)*
≤3·0 h	175 (22·2%)	166 (21·8%)	1·00 (0·81–1·24)
>3·0≤4·5 h	232 (16·9%)	229 (15·9%)	1·14 (0·95–1·36)
>4·5 h	201 (16·4%)	161 (13·8%)	1·22 (0·99–1·50)
Total 90-day mortality	**608 (17·9%)**	**556 (16·5%)**	**1·11 (0·99–1·25)**
Test for linear trend of log HR with increasing treatment delay (p=0·22)			



Lancet 2014; 384: 1929–35

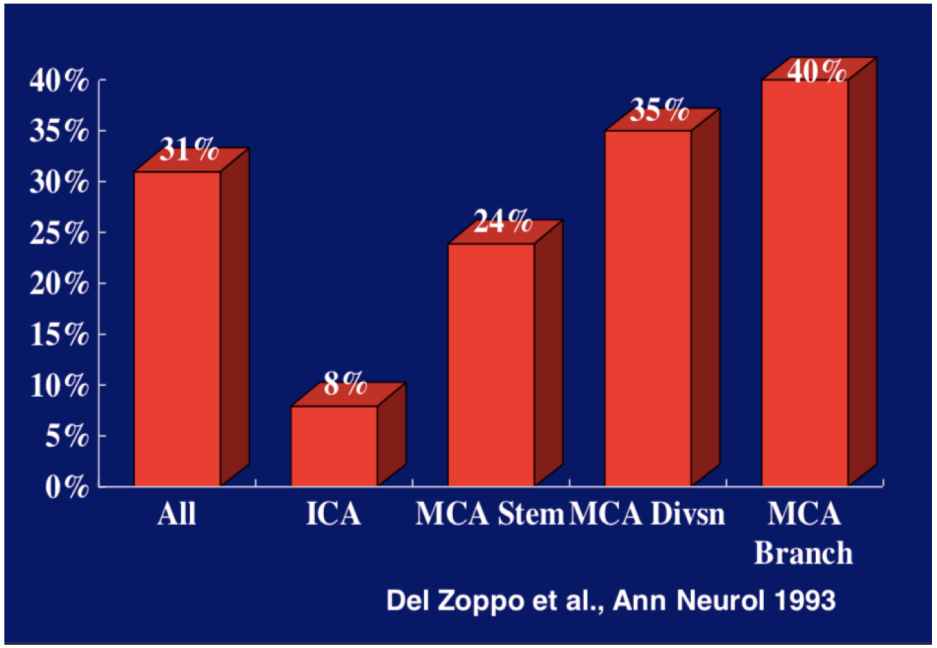
Emorragia cerebrale a 7gg

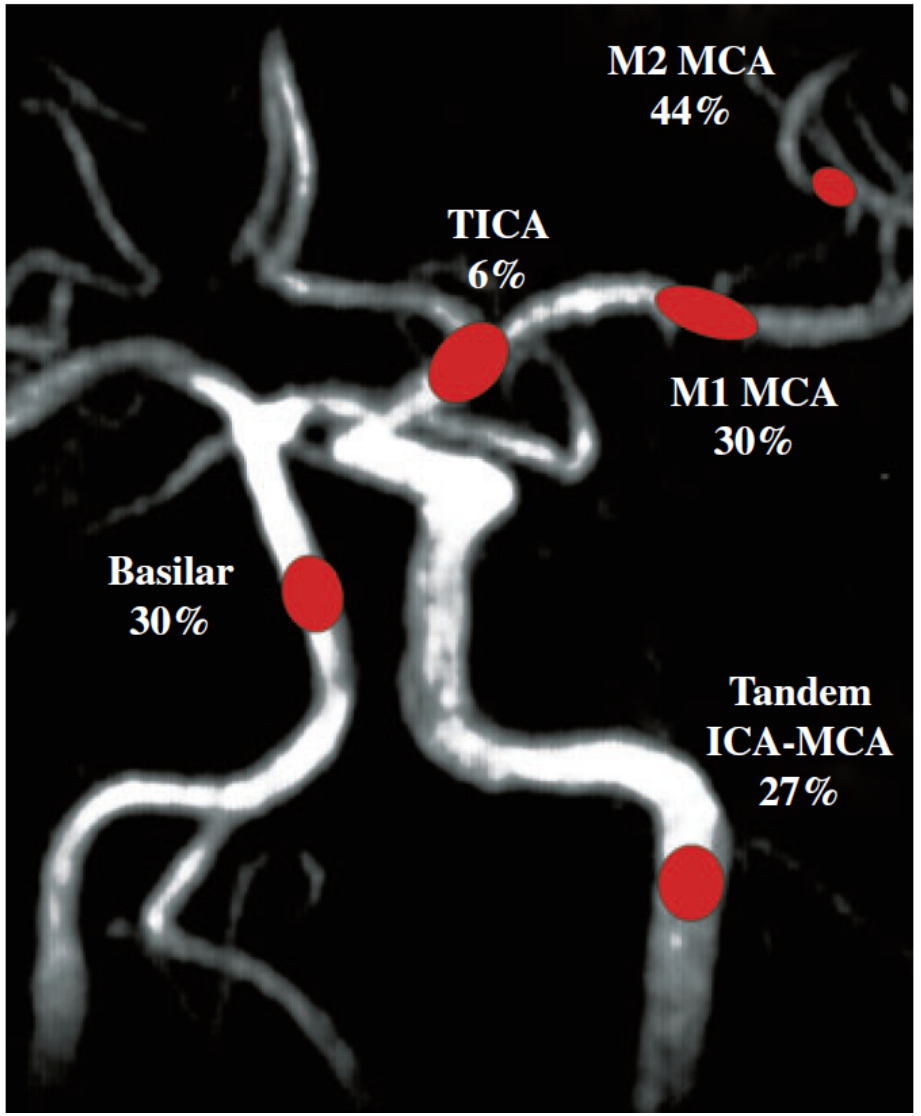


2·3% emorragie cerebrali fatali nella prima settimana

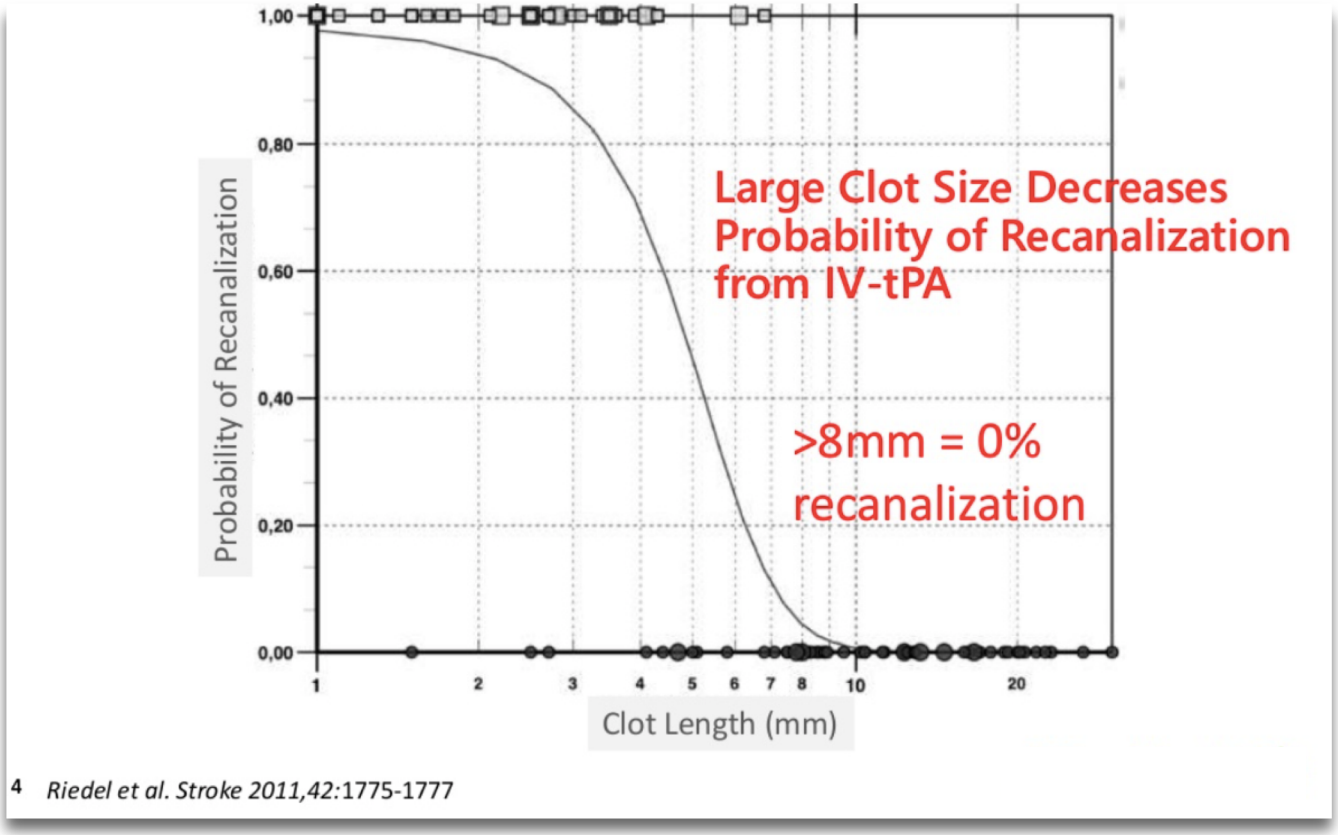
Lancet 2014; 384: 1929–35

% di ricanalizzazione un'ora dopo rtPA e.v. (AGF)





Ricanalizzazione



4 *Riedel et al. Stroke 2011,42:*1775-1777

- Lunghezza
- Età del coagulo
- Sede
- Aterotrombosi
- Composizione

Evidenze per la trombectomia meccanica nel 2015

5 Total Major Thrombectomy Trials Published in NEJM in 2015

	TICI 2b/3 rate	mRS 0-2 at 90 days	Death rate
MR CLEAN	59%	32.6% v. 19.1%	21% v 22%
ESCAPE	72%	53% v. 29%	10% v. 19%
EXTEND-IA	86%	71% v. 40%	9% v. 20%
SWIFT PRIME	88%	60% v. 36%	9% v. 12%
REVASCAT	66%	44% v 28%	18% v 16%

International Journal of Stroke 10, 1119-1129
August 2015

Guidelines

Intravenous thrombolysis and intra-arterial interventions in acute ischemic stroke: Italian Stroke Organisation (ISO)-SPREAD guidelines

Danilo Toni[1]*, Salvatore Mangiafico[2], Elio Agostoni[3], Mauro Bergui[4], Paolo Cerrato[5], Alfonso Ciccone[6], Stefano Vallone[7], Andrea Zini[8], and Domenico Inzitari[9]

Dalla controversia su alcuni criteri è derivata la dicotomia "controindicazioni assolute / relative"

Table 2 i.v. Thrombolysis: inclusion criteria

Patients of both sexes aged ≥18 years
Ischemic stroke responsible for a measurable language, motor, cognitive, visual perception deficit, and/or neglect
Onset of symptoms within 4·5 hours (at administration of rt-PA)
Symptoms present for at least 30 min. Symptoms should be distinguished from those of an episode of generalized ischemia (i.e. syncope), seizure, or migraine crisis
Patients (or family members) must have received treatment information and have given consent to the use of their data and to follow-up procedures

Table 3 i.v. Thrombolysis: absolute exclusion criteria

Stroke onset >4·5 hours
Intracranial hemorrhage on brain CT
Clinical suspicion of SAH, despite normal CT
Administration of i.v. heparin in the previous 48 h and aPTT above laboratory normal upper limit
Platelet count <100 000/mm^3
Known hemorrhagic diathesis
Current or recent severe bleeding
Suspected intracranial hemorrhage
Bacterial endocarditis, pericarditis
Acute pancreatitis
Neoplasm with increased hemorrhagic risk
Severe liver disease, including liver failure, cirrhosis, portal hypertension (esophageal varices), active hepatitis
Hemorrhagic retinopathy (e.g. changes in vision in diabetics)
Increased hemorrhagic risk due to comorbidity
Recent (<10 days) traumatic external heart massage, childbirth, puncture of noncompressible blood vessel (e.g. subclavian or jugular vein)
Ulcer disease of the gastrointestinal tract (<3 months)

International Journal of Stroke 10, 1119-1129 August 2015

Guidelines

Intravenous thrombolysis and intra-arterial interventions in acute ischem
Italian Stroke Organisation (ISO)-SPREAD guidelines

Danilo Toni[1]*, Salvatore Mangiafico[2], Elio Agostoni[3], Mauro Bergui[4], Paolo Cerrato[5]
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Table 4 i.v. Thrombolysis: relative exclusion criteria*

Mild deficit or rapidly improving symptoms (30 min)
Unknown time of onset or stroke present on awakening
Seizure at stroke onset
Patient with a history of stroke and concomitant diabetes
Blood glucose <50 or >400 mg/dl
History of stroke in the last three-months
Uncontrolled severe arterial hypertension
Clinically severe stroke (e.g. NIHSS > 25) and/or severe according to appropriate neuro-imaging techniques
Patient on oral anticoagulant treatment
Patient on anticoagulant treatment with low molecular weight heparins
History of CNS diseases: cancer, brain or spine surgery, aneurysm
History of intracranial hemorrhage (parenchymal or subarachnoid)
Pregnancy
Major surgery or severe trauma (<3 months)

*Reported in the summary of product characteristics of Actilyse but contradicted or not supported by literature.

Recommendations	Grade
Treatment with i.v. rt-PA (0·9 mg/kg, maximum dose 90 mg, 10% of the dose as bolus, the remainder in 60 min infusion) is recommended within 4·5 hours of onset of ischemic stroke, without upper limits of age and severity. However, treatment must be carried out as early as possible.	A
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with mild deficits or rapidly improving symptoms which are however still detectable at the time of starting treatment.	B
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with a history of prior stroke and diabetes.	B
Treatment with i.v. rt-PA is recommended in patients with unwitnessed stroke or stroke present on awakening, when advanced neuro-imaging (DW/PW MR or pCT) define an area of tissue mismatch and/or enable dating of the event within at least three-hours (compare DW with FLAIR MR).	D
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with focal neurological deficit onset with seizure, when there is clinical evidence, if necessary supported by neuro-imaging (DW/PW MR or PCT), that the residual neurological deficit is not a post-critical deficit but is attributable to a cerebral ischemia.	GPP
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with blood glucose <50 mg/dl and neurological deficit which persists after the restoration of normal blood glucose.	GPP
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with blood glucose > 400 mg/dl if, treated with s.c. or i.v. insulin, it drops below 200 mg/dl.	GPP
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with a history of stroke over the last three-months taking into account: the extension of the previous lesion and time interval since the first stroke (higher risk of hemorrhage for larger and more recent lesions), patient age (potential increased risk of bleeding with older age and risk/benefit ratio as a function of life expectancy), potential severity of the new event (also definable by means of neuro-imaging techniques such as MR DW/PW or pCT).	GPP
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with severe arterial hypertension after reaching the pressure range SBP < 185 and DBP < 110, which must be maintained during treatment and for 24 h after thrombolysis.	GPP
Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients on oral anticoagulant treatment with vitamin K antagonists and INR ≤ 1·7.	GPP

Ictus ad esordio indeterminato

14-27% degli ictus

- **DAWN trial** Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *Nogueira RG N Engl J Med. 2018 378 11-21.*

- **DEFUSE 3** Thrombectomy for stroke with perfusion imaging selection at 6–16 hours. *Albers GW et all N Engl J Med. 2018 378. 708-718*

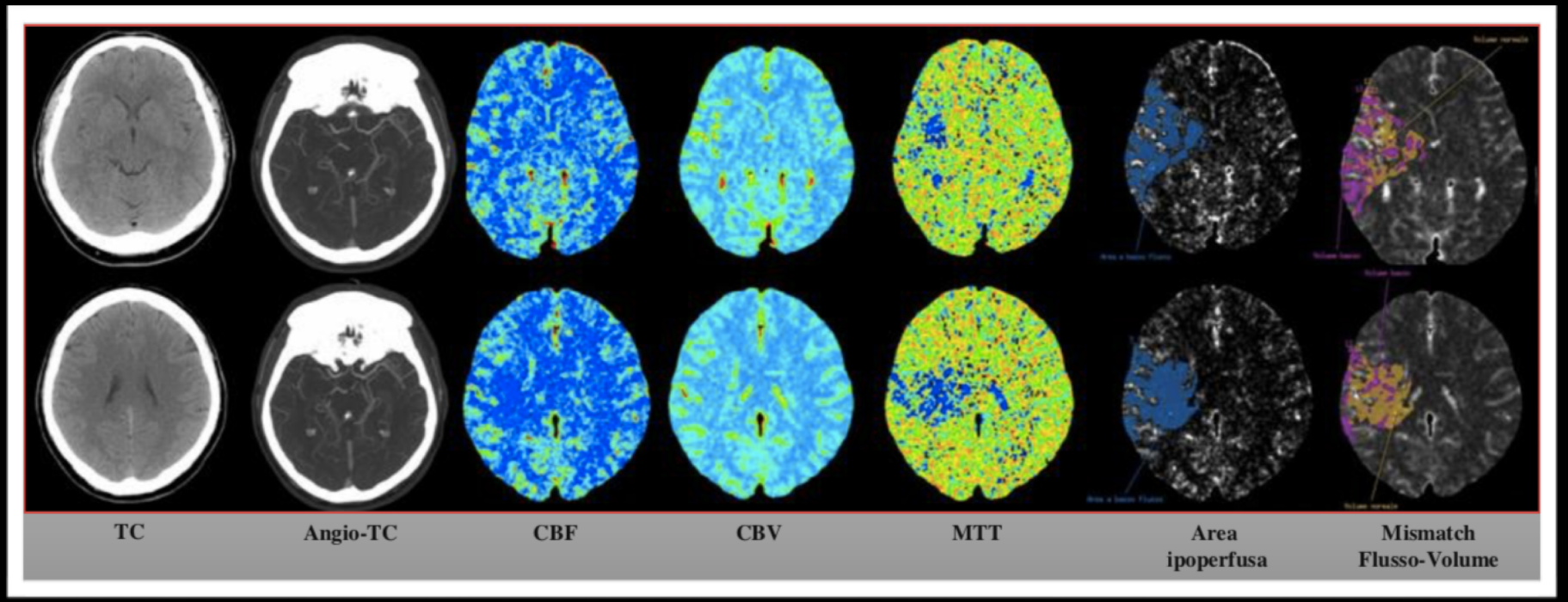
2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

From the American Heart Association/American Stroke Association. Powers W.J. Stroke 2018. 49.

"in pazienti selezionati con ictus ischemico acuto esordito tra 6 e 16 ore dall'ultima volta visti sani, con una occlusione di un grosso vaso del circolo anteriore che rispettano i criteri di eleggibilità degli studi DAWN e DEFUSE 3, è raccomandata la trombectomia meccanica" **(Classe di raccomandazione I e Livello di evidenza A)**

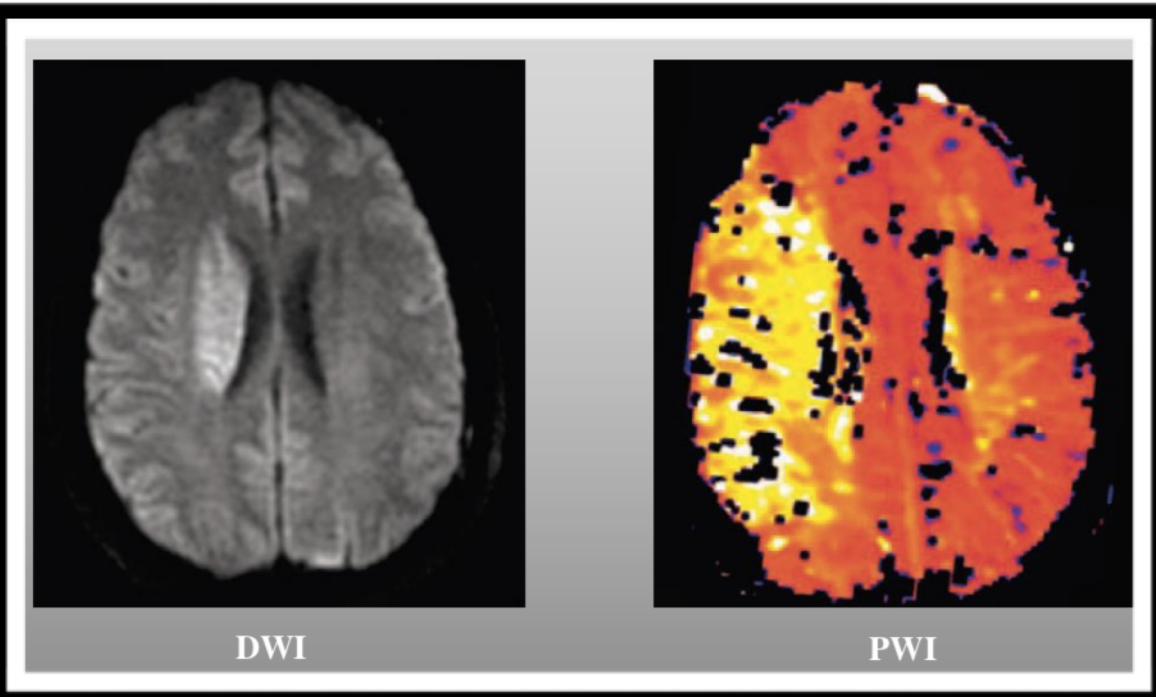
"in pazienti selezionati con ictus ischemico acuto esordito tra 6 e 24 ore dall'ultima volta in cui erano stati visti sani, con una occlusione di un grosso vaso del circolo anteriore che rispettano i criteri di eleggibilità dello studio DAWN, la trombectomia meccanica è ragionevole" (Classe di raccomandazione IIa e Livello di evidenza B-R)

TC/ANGIO TC/TC perfusionale



RM ENCEFALO

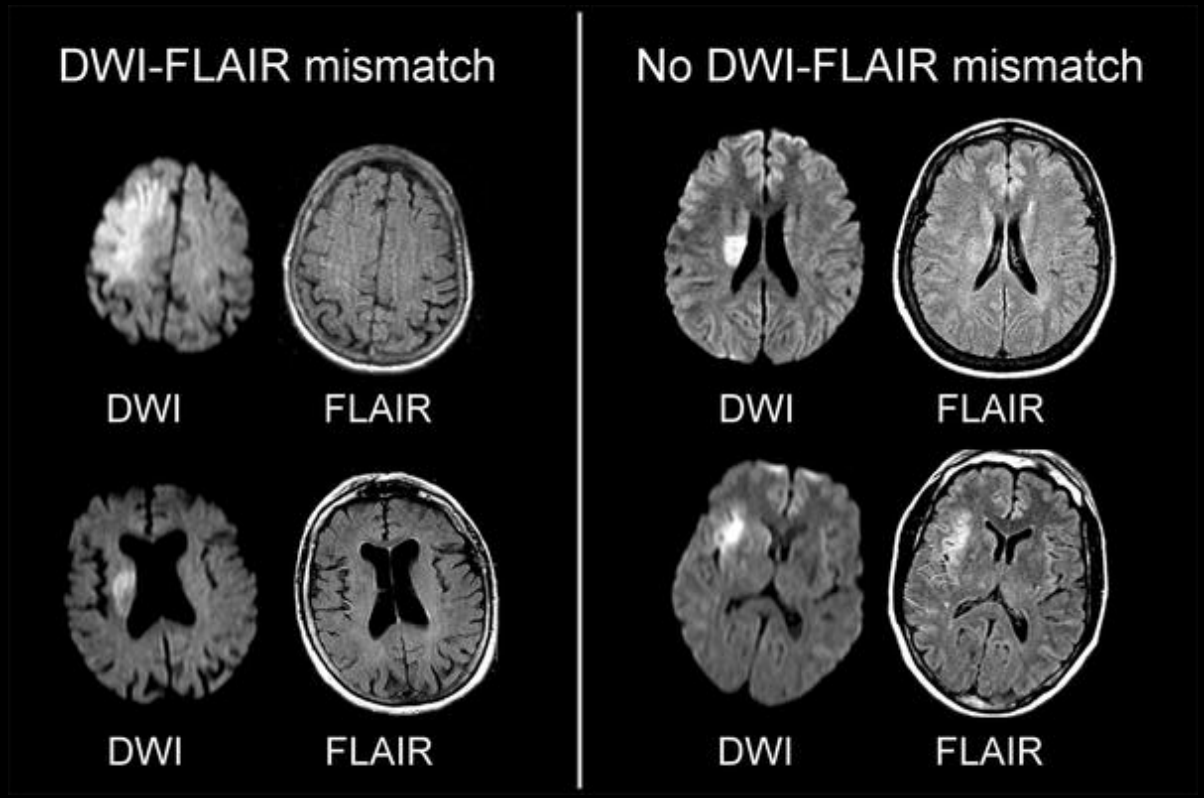
Il mismatch PWI > DWI



la differenza fra le dimensioni dell'area ipoperfusa alla PWI e del core ischemico alla DWI (mismatch PWI > DWI) rappresenta la penombra ischemica

RM encefalo mismatch DWI-FLAIR

Le immagini di Risonanza Magnetica nei pazienti con ictus ad esordio indeterminato, possono identificare la presenza di un lesione ischemica nelle immagini in DWI combinate con l'assenza di chiaro segnale iperintenso nella stessa regione in FLAIR, come predittore dell'esordio dei sintomi entro 4.5 ore.



Lo studio WAKE UP

The NEW ENGLAND JOURNAL of MEDICINE

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MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

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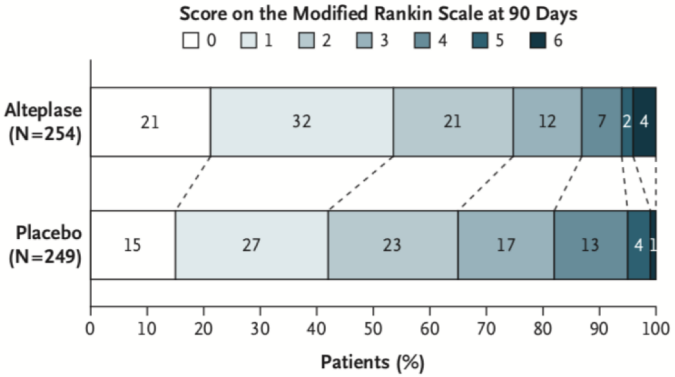
Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).* NIHSS media pari a 6

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1–3)	2 (1–3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0–11.0)	7.0 (2.0–14.0)	Mean difference ($\log_e$)	−0.04 (−0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	−0.52 (−0.88 to −0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7)	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8–17.7)	3.3 (1.1–16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶



mRS score medio a 90 giorni

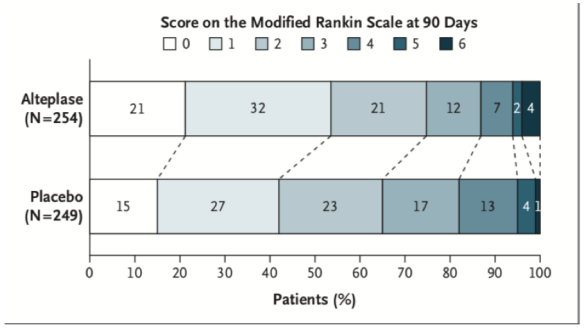
- 1 nel gruppo alteplase
- 2 nel gruppo placebo

(adjusted common odds ratio, 1.62; 95% CI, 1.17 - 2.23; P = .003).

Lo studio WAKE UP

Table 3. Safety Outcomes.

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
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		



La frequenza dell'emorragia intracranica sintomatica è risultata del 2.0% nel gruppo alteplase e dello 0.4% nel gruppo placebo (odds ratio, 4.95; 95% CI, 0.57 - 42.87; P = .15). **Il risultato della shift analysis evidenzia che il beneficio del trattamento supera il rischio di complicanze.**

Bassa dose di r-tPA (**0,6 mg/kg**)
15% della dose totale in bolo
il rimanente in infusione in 60 minuti

Il 40% degli ictus acuti sono in terapia anti aggregante piastrina

Recenti metanalisi di RTC e studi di coorte hanno riportato che l'uso di antiaggreganti piastrinici aumentano significativamente il rischio di emorragia cerebrale sintomatica

Pan X *Int J Stroke*. 2015;10:317–323.

In Giappone sono state approvate le basse dosi di trombolitico

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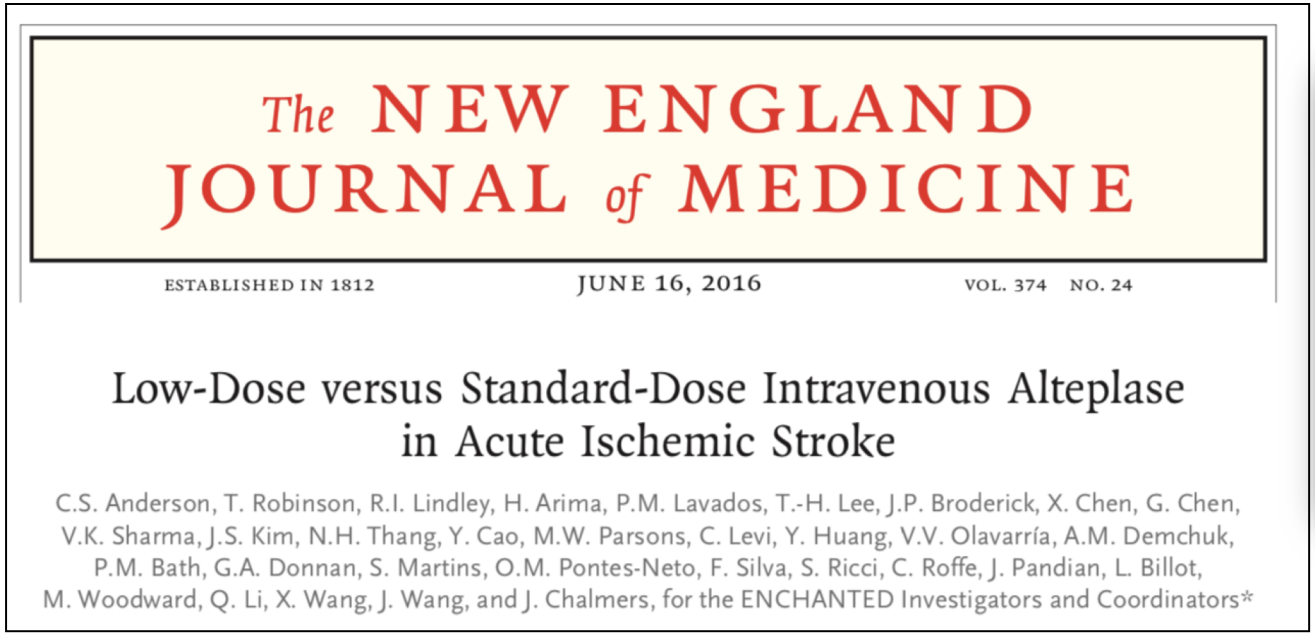

The NEW ENGLAND JOURNAL of MEDICINE

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Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke

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Non ha dimostrato la non inferiorità delle basse dosi rispetto alle dosi standard di r-TPA

Table 2. Primary and Secondary Outcomes at 3 Months.*

Outcome	Low-Dose Alteplase (N=1654)	Standard-Dose Alteplase (N=1643)	Odds Ratio with Low-Dose Alteplase (95% CI)	P Value†	P Value for Noninferiority‡
Primary outcome: death or disability — no./total no. (%)§	855/1607 (53.2)	817/1599 (51.1)	1.09 (0.95 to 1.25)		0.51
Secondary outcomes					
Symptomatic intracerebral hemorrhage — no. (%)					
By SITS-MOST criteria¶	17 (1.0)	35 (2.1)	0.48 (0.27 to 0.86)	0.01	
By NINDS criteria‖	98 (5.9)	131 (8.0)	0.73 (0.55 to 0.95)	0.02	
Score on the modified Rankin scale — no./total no. (%)			1.00 (0.89 to 1.13)**		0.04
0: No symptoms at all	403/1607 (25.1)	397/1599 (24.8)			
1: No substantive disability despite symptoms	349/1607 (21.7)	385/1599 (24.1)			
2: Slight					
3: Mode					
4: Mode livin					
5: Sever					
6: Death					
Death or m					
Death withi					
Overall hea					
Admission					
Median dur					
Death or ne					
Serious adv					

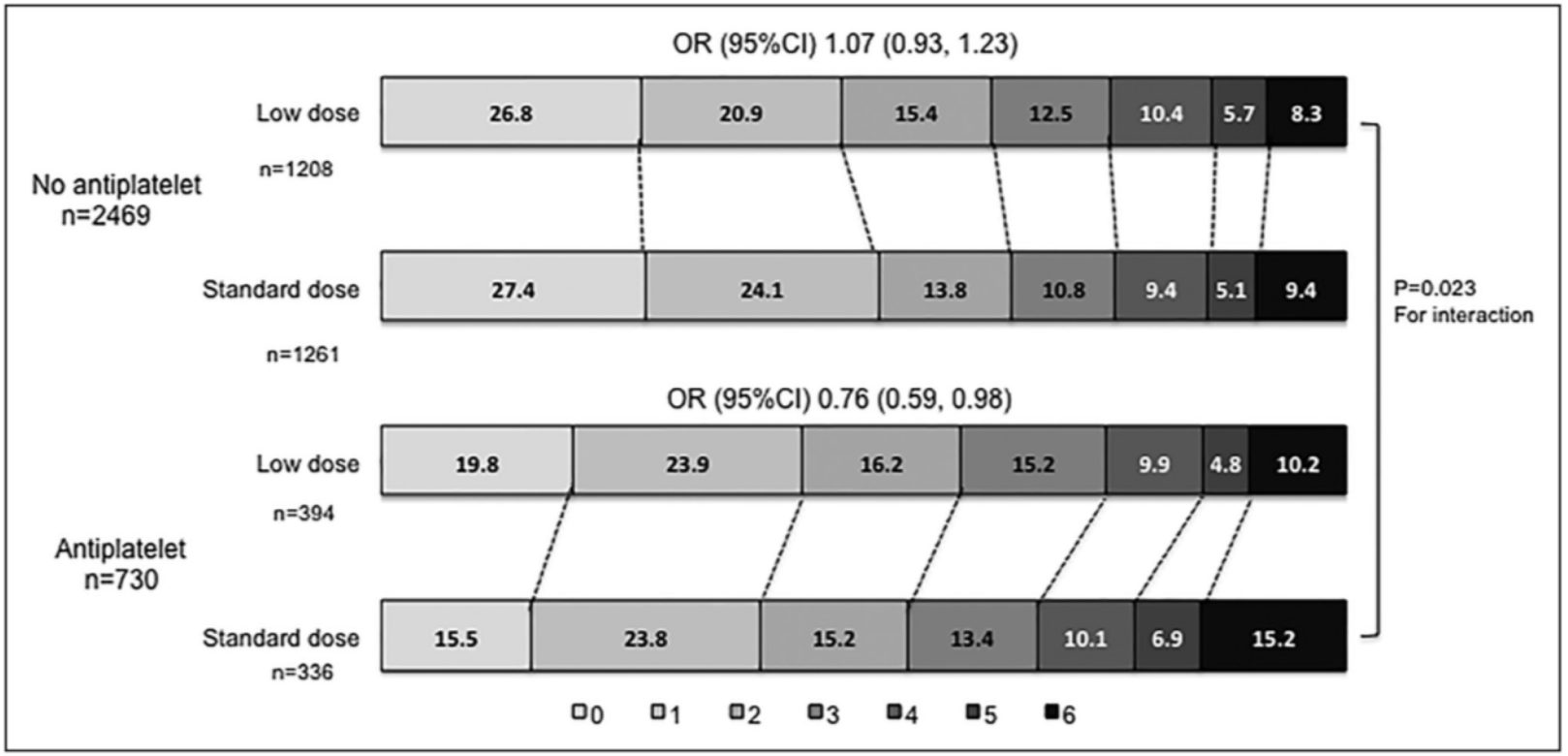


Figure 1. Global functional outcome at 90 days in patients with and without prior antiplatelet therapy by randomized treatment. The figure shows the raw distribution of scores on the modified Rankin Scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms; 1, symptoms without clinical significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. Unadjusted odds ratios (ORs; and 95% confidence intervals [CIs]) are provided for ordinal shift of mRS between low- and standard-dose intravenous alteplase by patients with and without prior use of antiplatelet therapy and acute ischemic stroke.

Raccomandazione 9.16 **Forte contro**

Non è indicata la somministrazione della dose bassa di r-tPA (0,6 mg/kg) nella generalità dei pazienti con ictus ischemico acuto.

Raccomandazione 9.17 **GPP***

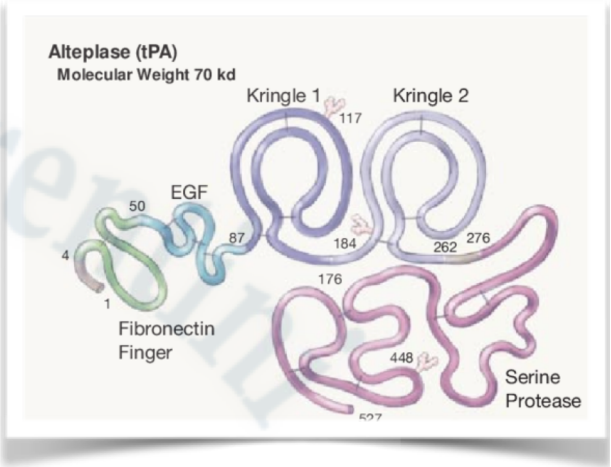
Il Gruppo ISO-SPREAD suggerisce la possibilità di ricorrere alla bassa dose di r-tPA (0,6 mg/kg e.v., di cui il 15% della dose totale in bolo e il rimanente in infusione in 60 minuti) nei pazienti in trattamento con antiaggreganti piastrinici, in particolare in caso di doppia antiaggregazione.

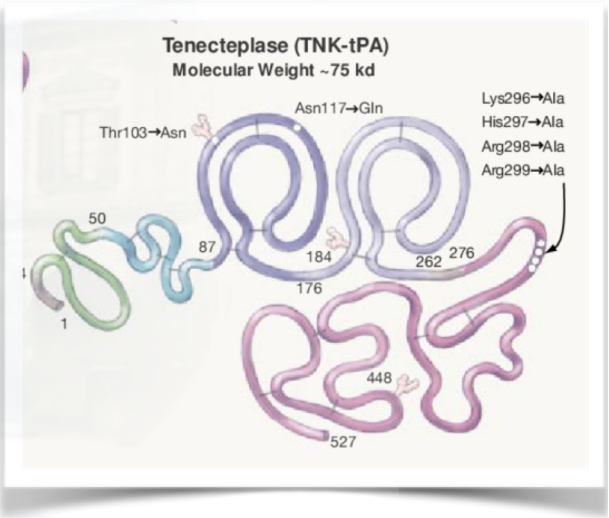
Dosaggio della trombolisi

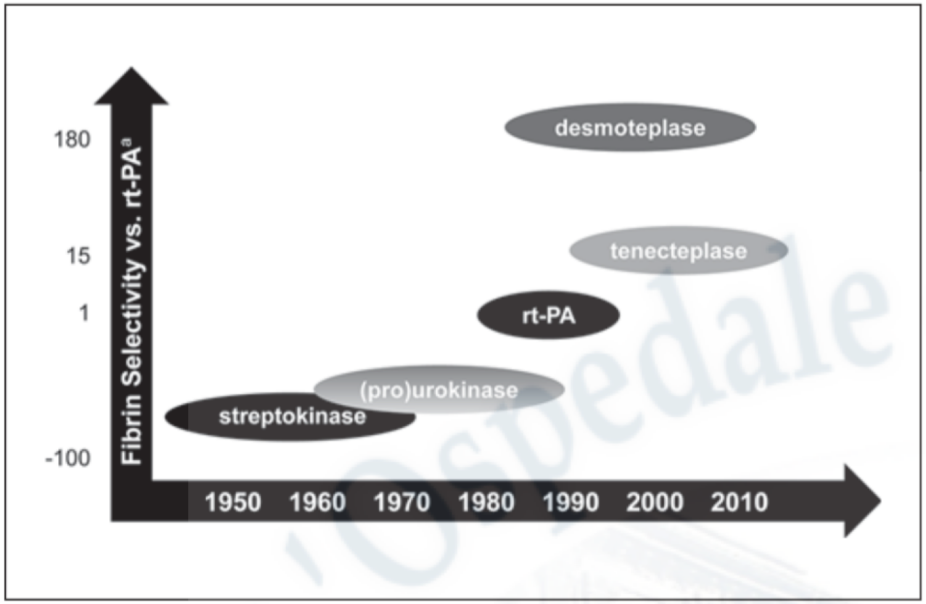
I risultati sostanzialmente negativi dello studio ENCHANTED hanno consentito di rafforzare il messaggio relativo alla necessità di impego della trombolisi al dosaggio universalmente consigliato (0,9 mg/kg), ma la significativa riduzione, in una analisi di sottogruppo prespecificata, relativamente all'outcome funzionale (valutato tenendo conto dei vari gradi della scala Rankin), **risultata favorevole della bassa dose di r-tPA (0,6 mg/kg) nel gruppo pretrattato con antipiastinici** rispetto al gruppo dei non trattati con antiaggreganti (p=0.02), induce a considerare, in questa tipologia di pazienti, l'utilizzo della bassa dose, piuttosto che la non somministrazione in assoluto della trombolisi.

Confronto tra trombolitici

Agent	Half-life (min	Fibrin selectivity	PAI-1 inhibition
Urokinase	15	-	+++
Alteplase	4-8	++	+++
Staphylokinase	6	---	-
Monteplase	23	+/-	+++
Pamiteplase	30-47	++	+++
Lanoteplase	23-37	+	-
Reteplase	14-18	+	++
Tenecteplase	11-20	+++	-
Desmoteplase	138	+++++	?







Selettività per la fibrina

…treatment with intravenous 90 µg/kg desmoteplase administered 3 to 9 hours after stroke onset in patients with proven cerebral artery occlusions **did not significantly increase favorable clinical outcomes**, although it modestly increased arterial recanalization with no increased rate of SICH

Major Clinical Trials

Desmoteplase 3 to 9 Hours After Major Artery Occlusion Stroke

The DIAS-4 Trial (Efficacy and Safety Study of Desmoteplase to Treat Acute Ischemic Stroke)

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Background and Purpose—The DIAS-3 trial (Efficacy and Safety Study of Desmoteplase to Treat Acute Ischemic Stroke [phase 3]) did not demonstrate a significant clinical benefit of desmoteplase administered 3 to 9 hours after stroke in patients with major artery occlusion. We present the results of the prematurely terminated DIAS-4 trial together with a post hoc pooled analysis of the concomitant DIAS-3, DIAS-4, and DIAS-J (Japan) trials to better understand the potential risks and benefits of intravenous desmoteplase for the treatment of ischemic stroke in an extended time window.

Methods—Ischemic stroke patients with occlusion/high-grade stenosis in major cerebral arteries were randomly assigned to intravenous treatment with desmoteplase (90 µg/kg) or placebo. The primary outcome was modified Rankin Scale (mRS) score of 0 to 2 at day 90. Safety assessments included mortality, symptomatic intracranial hemorrhage, and other serious adverse events.

Results—In DIAS-4, 52 of 124 (41.9%) desmoteplase-treated and 46 of 128 (35.9%) placebo-treated patients achieved an mRS score of 0 to 2 (odds ratio, 1.45; 95% confidence interval, 0.79; 2.64; *P*=0.23) with equal mortality, frequency of symptomatic intracranial hemorrhage, and other serious adverse events in both the treatment arms. In the pooled analysis, mRS score of 0 to 2 was achieved by 184 of 376 (48.9%) desmoteplase-treated versus 171 of 381 (44.9%) placebo-treated patients (odds ratio, 1.33; 95% confidence interval, 0.95; 1.85; *P*=0.096). Treatment with desmoteplase was safe and increased the recanalization rate (107/217 [49.3%] versus 85/222 [38.3%]; odds ratio, 1.59; 95% confidence interval, 1.08–2.35; *P*=0.019). Recanalization was associated with favorable outcomes (mRS 0–2) at day 90 in both the treatment arms.

Conclusions—Late treatment with intravenous 90 µg/kg desmoteplase is safe, increases arterial recanalization, but does not significantly improve functional outcome at 3 months.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00856661.

(*Stroke*. 2016;47:2880-2887. DOI: 10.1161/STROKEAHA.116.013715.)

Tenecteplase Knocking on the Door
The EXTEND-IA TNK Trial

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Stroke. 2018;49:2276-2277

Published Ahead of Print on June 2, 2017 as 10.1212/WNL.0000000000004062

Tenecteplase in ischemic stroke offers improved recanalization

Analysis of 2 trials

Andrew Bivard, PhD*

ABSTRACT

Il gruppo di trattamento TNK con occlusione completa (TICI 0/1)

- miglior tasso di ricanalizzazione (71% vs 43%, p<0,001),
- miglior recupero neurologico a 24 ore (miglioramento medio dell'NIHSS di 9 punti vs 1, p<0,001),
- più alto tasso di outcome favorevole a 3 mesi (OR per mRS 0/1 con TNK: 4,82, IC: 1,02-7,48, p=0,05),
- ridotta percentuale di trasformazione emorragica (3% vs 7%, p=0,002)
- ridotta percentuale di emorragia sintomatica (0% vs 3%, p=0,04)

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial

Nicola Logallo, Vojtech Novotny, Jörg Assmus, Christopher E Kvistad, Lars Alteheld, Ole Morten Rønning, Bente Thommessen, Karl-Friedrich Amthor, Hege Ihle-Hansen, Martin Kurz, Håkon Tobro, Kamaljit Kaur, Magdalena Stankiewicz, Maria Carlsson, Åse Morsund, Titto Idicula, Anne Hege Aamodt, Christian Lund, Halvor Næss, Ulrike Waje-Andreassen, Lars Thomassen

Summary

Background Tenecteplase is a newer thrombolytic agent with some pharmacological advantages over alteplase. *Lancet Neurol* 2017; 16: 781–88

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.

Studio di superiorità randomizzato, in aperto, con endpoint ciechi, condotto in 13 stroke units in Norvegia

Tenecteplase (0,4 mg/kg; max. 40 mg) vs
Alteplase 0,9 mg/kg (fino a un massimo di 90 mg)

1.100 pazienti
Età media 77 anni
NIHSS basale media = 4

mRankin 0/1 a 3 mesi è stato ottenuto da 354 (64%) pazienti nel gruppo tenecteplase e in 345 (63%) nel gruppo alteplase (odds ratio: 1,08; 95% CI 0 84-1 38, p = 0 52).

Mortalità a 3 mesi 5% nei due gruppi

tenecteplase 0,4 mg/kg ha un profilo di sicurezza simile a quello di alteplase 0,9 mg/kg

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EXTEND-IA TNK

Tenecteplase (0,25 mg/kg; max. 25 mg)

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

Table 1. Characteristics of the 202 Patients at Baseline.*

Characteristic	Tenecteplase Group (N=101)	Alteplase Group (N=101)
Age — yr	70.4±15.1	71.9±13.7
Male sex — no. (%)	58 (57)	52 (51)
Median NIHSS score (IQR)†	17 (12–22)	17 (12–22)
Cause of stroke — no. (%)		
Cardioembolic occlusion	46 (46)	54 (53)
Large-artery occlusion	21 (21)	18 (18)
Undetermined or other	34 (34)	29 (29)
Median time from stroke onset to hospital arrival (IQR) — min	60 (44–89)	72 (53–104)
Median time from stroke onset to initiation of intravenous thrombolysis (IQR) — min	125 (102–156)	134 (104–176)
Median time from initiation of intravenous thrombolysis to arterial puncture (IQR) — min	43 (25–57)	42 (30–63)
Median time from initiation of intravenous thrombolysis to initial angiographic assessment (IQR) — min	54 (34–67)	56 (40–77)
Interhospital transfer for thrombectomy — no. (%)	27 (27)	23 (23)
Site of vessel occlusion — no. (%)		
Internal carotid artery	24 (24)	24 (24)
Basilar artery	3 (3)	3 (3)
Middle cerebral artery		
First segment	59 (58)	60 (59)
Second segment	15 (15)	14 (14)
Median volume at initial imaging (IQR) — ml‡		
Ischemic core	14 (0–33)	11 (0–24)
Perfusion lesion	145 (105–175)	134 (103–170)

- Studio prospettico open-label, con valutazione in cieco
- 202 pazienti con ictus ischemico con indicazione alla trombectomia per occlusione
  - carotide interna
  - arteria basilare
  - arteria cerebrale media

Outcome primario: riperfusione >50% o l'assenza di trombo rilevabile all'angiografia;
Outcome secondario: esito funzionale a 90 giorni valutato con la scala modificata di Rankin.

EXTEND-IA TNK

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

L'outcome primario si è verificato nel 22% dei pazienti trattati col tenecteplase e nel 10% di quelli trattati con l'alteplase (differenza 12%; IC95% 2-21).

L'esito neurologico è risultato migliore dopo trattamento col tenecteplase (punteggio mRS=2) che con l'alteplase (punteggio mRS=3; OR 1,7; IC95% 1,0-2,8; P=0,04).

Quattro studi in corso di fase III che usano il **tenecteplase 0.25 mg/kg**

- **TASTE study**
- **ATTEST-2**
- **TEMPO-2 study**
- **TWIST study**

Conclusioni

- Efficacia di una terapia personalizzata
- Non fermarsi di fronte agli ostacoli apparenti
- Time is brain
- Diffusione
- Formazione