II MEETING DELLE NEUROSCIENZE TOSCANE

Società dei Neurologi, Neurochirurghi e Neuroradiologi Ospedalieri

SOCIETÀ ITALIANA DI NEUROLOGIA

Trombolisi sistemica: l'evoluzione dei criteri di inclusione

Dr.ssa Raffaella Valenti
Ospedale S. Stefano, Prato
ASL Toscana Centro

Firenze – 7 Aprile 2018

Trombolisi sistemica: l'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
- ✓ Minime variazioni negli anni
- ✓ Criteri di Inclusione ISO SPREAD 2016
- ✓ Criteri di Inclusione LLGG AHA/ASA 2018
- ✓ Dalla controversia su alcuni criteri è derivata la dicotomia "controindicazioni assolute / relative"

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P<0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P=0.30$).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. N Engl J Med 1995

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DALLE SINDROMI ALLE MALATTIE NEUROLOGI
RICERCA TRASLAZIONALE, APPROPRIATEZZA
DIAGNOSTICA E TERAPEUTICA

ORIGINAL CONTRIBUTION

Recombinant Tissue-Type Plas
Activator (Alteplase) for Ische
3 to 5 Hours After Symptom C

The ATLANTIS Study: A Randomized Co

Wayne M. Clark, MD
Stanley Wissman, MD†
Gregory W. Albers, MD
Jack H. Jhamandas, MD, PhD
Kenneth P. Madden, MD, PhD
Scott Hamilton, PhD
for the ATLANTIS Study Investigators

Context Recombinant tissue-type plasminogen a
comes for patients with acute ischemic stroke, but cu
within 3 hours of symptom onset. This restricts the r
treated, since most stroke patients present more thar

Objective To test the efficacy and safety of rt-PA
stroke when administered between 3 and 5 hours aft

Design The Alteplase ThromboLysis for Acute Nonin
Stroke (ATLANTIS) study is a phase 3, placebo-controlle
conducted between December 1993 and July 1998, w

Original Contributions

Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke

The European Cooperative Acute Stroke Study (ECASS)

Werner Hacke, MD; Markku Kaste, MD; Cesare Fieschi, MD; Danilo Toni, MD; Emmanuel Lesaffre, PhD; Rüdiger von Kummer, MD; Gudrun Boysen, MD; Erich Bluhmki, BSC; Godehard Höxter, BSc; Marie-Helene Mahagne, MD; Michael Hennerici, MD; for the ECASS Study Group

Objective.—To evaluate the efficacy and safety of intravenous thrombolysis using recombinant tissue plasminogen activator (rt-PA) in patients with acute ischemic stroke.

Design.—Randomized, prospective, multicenter, double-blind, placebo-controlled clinical trial.

Setting.—A total of 75 hospitals in 14 European countries.

Patients.—A total of 620 patients with acute ischemic hemispheric stroke and moderate to severe neurologic deficit and without major early infarct signs on initial computed tomography (CT).

Interven
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symptoms.

THROMBOLYTIC therapy has been used in patients with acute ischemic stroke to restore cerebral blood flow, reduce ischemia, and limit neurologic disability.[1] The hypothesis is that recanalization of an occluded cerebral artery may assist the recovery of reversibly ischemic tissue.[2,3] During the past decade several thrombolytic substances have been tested in uncontrolled trials,

ARTICLES

Articles

Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)

*Werner Hacke, Markku Kaste, Cesare Fieschi, Rüdiger von Kummer, Antoni Davalos, Dieter Meier, Vincent Larrue, Erich Bluhmki, Stephen Davis, Geoffrey Donnan, Dietmar Schneider, Exuperio Diez-Tejedor, Paul Trouillas, for the Second European-Australasian Acute Stroke Study Investigators**

Summary

Background Thrombolysis for acute ischaemic stroke has been investigated in several clinical trials, with variable results. We have assessed the safety and efficacy of intravenous thrombolysis with alteplase (0·9 mg/kg bodyweight) within 6 h of stroke onset.

Methods This non-angiographic, randomised, double-blind, trial enrolled 800 patients in Europe, Australia, and New

Interpretation The results do not confirm a statistical benefit for alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial haemorrhage, thrombolysis with alteplase at a dose of 0·9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome.

Lancet 1998; **352:** 1245–51

See Commentary page ????

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6-7-8 APRILE 2018
FIRENZE

CENTRO DIDATTICO MORGAGNI
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Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study

Nils Wahlgren, Niaz Ahmed, Antoni Dávalos, Gary A Ford, Martin Grond, Werner Hacke, Michael G Hennerici, Markku Kaste, Sonja Kuelkens, Vincent Larrue, Kennedy R Lees, Risto O Roine, Lauri Soinne, Danilo Toni, Geert Vanhooren, for the SITS-MOST investigators

Summary

Background The aim of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was to assess the safety and efficacy of intravenous alteplase as thrombolytic therapy within the first 3 h of onset of acute ischaemic stroke. Under European Union regulations, SITS-MOST was required to assess the safety profile of alteplase in clinical practice by comparison with results in randomised controlled trials.

Methods 6483 patients were recruited from 285 centres (50% with little previous experience in stroke thrombolysis) in 14 countries between 2002 and 2006 for this prospective, open, monitored, observational study. Primary outcomes were symptomatic (a deterioration in National Institutes of Health stroke scale score of ≥4) intracerebral haemorrhage type 2 within 24 h and mortality at 3 months. We compared mortality, the proportion of patients with symptomatic intracerebral haemorrhage as per the Cochrane definition, and functional outcome at 3 months with relevant pooled results from randomised controlled trials.

Findings Baseline characteristics of patients in SITS-MOST were much the same as those in the pooled randomised controlled trials. At 24 h, the proportion of patients with symptomatic intracerebral haemorrhage (per the SITS-MOST protocol) was 1·7% (107/6444; 95% CI 1·4–2·0); at 7 days, the proportion with the same condition as per the Cochrane definition was 7·3% (468/6438; 6·7–7·9) compared with 8·6% (40/465; 6·3–11·6) in the pooled randomised controlled trials. The mortality rate at 3 months in SITS-MOST was 11·3% (701/6218; 10·5–12·1) compared with 17·3% (83/479; 14·1–21·1) in the pooled randomised controlled trials.

Interpretation These data confirm that intravenous alteplase is safe and effective in routine clinical use when used within 3 h of stroke onset, even by centres with little previous experience of thrombolytic therapy for acute stroke. The findings should encourage wider use of thrombolytic therapy for suitable patients treated in stroke centres.

Lancet 2007; 369: 275–82

See Comment page 249

Department of Neurology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden (Prof N Wahlgren MD, N Ahmed MD); Department of Neurosciences, Hospital Germans Trias i Pujol, Universitat Autonoma de Barcelona, Barcelona, Spain (Prof A Dávalos MD); Freeman Hospital Stroke Service, Newcastle General Hospital, Newcastle upon Tyne, UK (Prof G A Ford FRCP); Kreisklinikum Siegen, Siegen, Germany (Prof M Grond MD); Department of Neurology, University of Heidelberg, Mannheim, Germany (Prof M G Hennerici MD); Department of Neurology, University of Heidelberg, Heidelberg, Germany (Prof W Hacke MD, S Kuelkens MD); Department of Neurology, Helsinki

Wahlgren N, Lancet 2007

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Sin

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

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Interpretation These data confirm that intravenous alteplase is safe and effective in routine clinica within 3 h of stroke onset, even by centres with little previous experience of thrombolytic therapy for findings should encourage wider use of thrombolytic therapy for suitable patients treated in stroke c

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.68). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

Hacke W, NEJM 2008

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

The IST-3 collaborative group*

Lancet 2012; 379: 2352–63
Published Online May 23, 2012
DOI:10.1016/S0140-6736(12)60768-5

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 24, 2012

See Comment page 2320
See Articles page 2364

*Members listed in the appendix
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peter.sandercock@ed.ac.uk

Summary

Background age and are wider rang

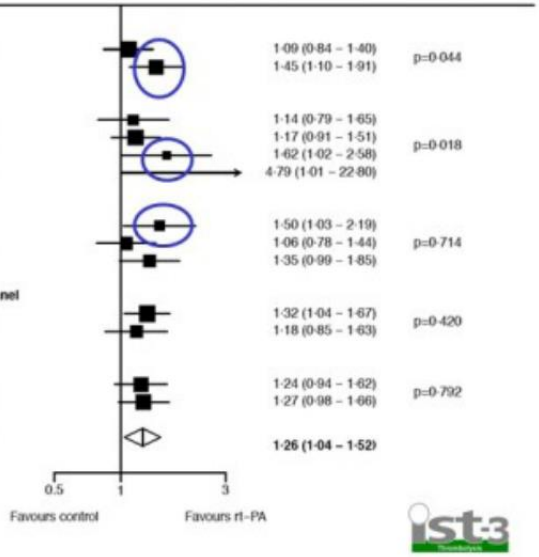
Methods In intravenou proportion The study i

Findings 3 analyses (1 At 6 month (OHS 0–2; 95% CI–2 p=0·001). rt-PA grou 95% CI 44– adjusted O 6 months t in total, ha

Interpretation For the types of patient recruited in IST-3, despite the early hazards, thrombolysis within 6 h improved functional outcome. Benefit did not seem to be diminished in elderly patients.

Effect on shift of OHS categories: Adjusted ordinal analyses

Subgroup	Events / No. patients rt-PA	Control	Adjusted Odds Ratio (99% CI)	Adjusted p value
Age (years)				
≤80	331 / 698 (47·4%)	346 / 719 (48·1%)	1·09 (0·84 – 1·40)	p=0·044
>80	223 / 817 (27·3%)	188 / 799 (23·5%)	1·45 (1·10 – 1·91)	
NIHSS score				
0 – 5	221 / 304 (72·7%)	232 / 308 (75·3%)	1·14 (0·79 – 1·65)	
6 – 14	276 / 728 (37·9%)	268 / 724 (37·0%)	1·17 (0·91 – 1·51)	p=0·018
15 – 24	50 / 402 (12·4%)	33 / 421 (7·8%)	1·62 (1·02 – 2·58)	
≥25	7 / 81 (8·6%)	1 / 65 (1·5%)	4·79 (1·01 – 22·80)	
Time to randomisation (hours)				
0 – 3	132 / 431 (30·6%)	95 / 418 (22·7%)	1·50 (1·03 – 2·19)	
3 – 4.5	182 / 577 (31·5%)	226 / 600 (37·7%)	1·06 (0·78 – 1·44)	p=0·714
>4.5	240 / 507 (47·3%)	213 / 500 (42·6%)	1·35 (0·99 – 1·85)	
Acute ischaemic change on randomisation scan according to expert panel				
No	392 / 883 (44·4%)	379 / 910 (41·6%)	1·32 (1·04 – 1·67)	p=0·420
Yes	158 / 624 (25·3%)	149 / 598 (24·9%)	1·18 (0·85 – 1·63)	
Treatment with antiplatelet drugs in previous 48 hours				
No	288 / 736 (39·1%)	282 / 725 (38·9%)	1·24 (0·94 – 1·62)	p=0·792
Yes	265 / 775 (34·2%)	251 / 786 (31·9%)	1·27 (0·98 – 1·66)	
Total	**554 / 1515 (36·6%)**	**534 / 1518 (35·2%)**	**1·26 (1·04 – 1·52)**	



hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

The IST-3 collaborative group, Lancet 2012

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Interaction: χ^2_1=5·80 (p=0·016)

Odds ratio (95% CI)

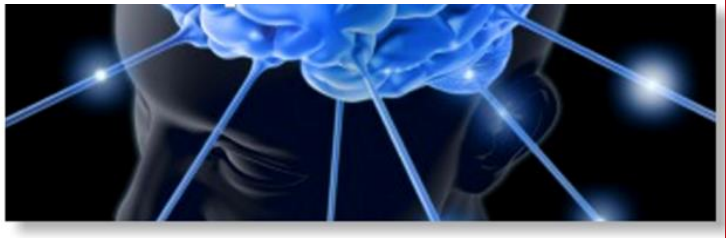
	Alteplase (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤3·0 h	22/787 (2·8%)	2/762 (0·3%)	10·86 (2·54–46·41)
>3·0≤4·5 h	35/1375 (2·5%)	7/1437 (0·5%)	5·63 (2·49–12·76)
>4·5 h	34/1229 (2·8%)	4/1166 (0·3%)	8·16 (2·88–23·11)
Age (years)			
≤80	59/2512 (2·3%)	9/2515 (0·4%)	6·93 (3·42–14·02)
>80	32/879 (3·6%)	4/850 (0·5%)	7·95 (2·79–22·60)
Baseline NIHSS score			
0–4	3/345 (0·9%)	0/321 (0·0%)	NE
5–10	20/1281 (1·6%)	5/1252 (0·4%)	3·90 (1·46–10·44)
11–15	23/794 (2·9%)	1/808 (0·1%)	24·14 (3·25–179·32)
16–21	24/662 (3·6%)	5/671 (0·7%)	5·00 (1·89–13·20)
≥22	21/309 (6·8%)	2/313 (0·6%)	10·94 (2·54–47·15)
All patients	**91/3391 (2·7%)**	**13/3365 (0·4%)**	**7·14 (3·98–12·79)**

0·5 1 2 4 8 16 32

Alteplase better

Alteplase worse

ISO
ITALIAN STROKE ORGANIZATION



ICTUS ACUTO: FASE DI OSPEDALIZZAZIONE

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.

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Trombolisi sistemica: criteri di inclusione

In sintesi

Trombolisi endovenosa: criteri di inclusione

Pazienti di ambo i sessi di età ≥18 anni
Ictus ischemico responsabile di un deficit misurabile di linguaggio, motorio, cognitivo, di sguardo, del visus e/o di neglect
Inizio dei sintomi entro 4.5 ore (alla somministrazione di rt-PA)
Sintomi presenti per almeno 30 minuti. I sintomi vanno distinti da quelli di un episodio di ischemia generalizzata (cioè una sincope), di una crisi epilettica o di una crisi di emicrania
I pazienti (o un familiare) debbono aver ricevuto informazione sul trattamento e aver dato il consenso all'utilizzo dei loro dati e alle procedure di follow-up

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

Endorsed by the Society for Academic Emergency Medicine

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair;

American Heart Association | American Stroke Association

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Eligibility Recommendations for IV Alteplase in Patients With AIS

Indications (Class I)	
Within 3 h*	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*Class I; LOE A*)
Additional recommendations for treatment with IV alteplase for patients with AIS (Class II)	
Extended 3- to 4.5-h window	For patients >80 y of age presenting in the 3- to 4.5-h window, IV alteplase is safe and can be as effective as in younger patients.† (*Class IIa; LOE B-NR*)‡
	For patients with mild but disabling stroke symptoms, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms, in the opinion of the treating physician, from treatment with IV alteplase because there is proven clinical benefit for those patients.† (*Class I; LOE B-R*)‡
3–4.5 h*	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*Class I; LOE B-R*)‡
Age Diabetes mellitus Prior stroke Severity OACs Imaging	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory.† (*Class I; LOE B-R*)‡

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Outcome after stroke thrombolysis in patients >80 years treated within 3 hours vs >3–4.5 hours

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Kennedy R. Lees, MD, FRCP
Peter A. Ringleb, MD
Christopher Bladin, MD
David Collas, MD, FRCP
Danilo Toni, MD, PhD
Gary A. Ford, MD, FRCP
And the SITS Investigators

ABSTRACT

Objective: T
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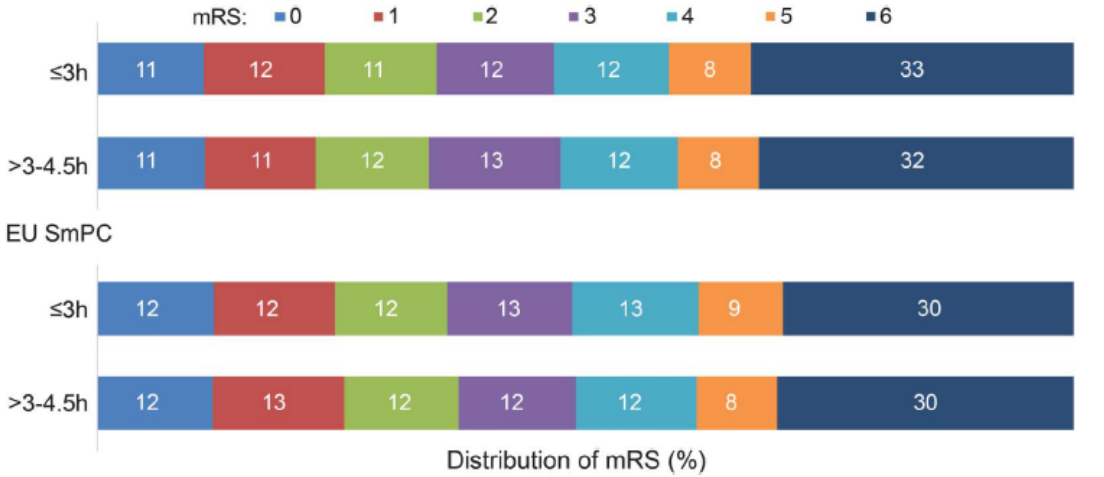
Safe Imple

Methods: A
with IVT ≤4
hours) were
(EU SmPC)
Rankin Sca
sults were

Figure 3 Distribution of mRS scores at 3 months in all patients >80 years and in patients >80 years old treated according to other EU SmPC criteria categorized by stroke OTT



EU SmPC = European Summary of Product Characteristics; mRS = modified Rankin Scale; OTT = onset to treatment time.

Ahmed, Neurology 2017

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Effects of alteplase for acute stroke according to cr… European Unio… marketing auth… patient-data me… trials

Werner Hacke[1], Patric… Colin Baigent[3,4], Lisa B… Erich Bluhmki[6], Thoma… Stephen M Davis[9], Geo… George Howard[12], Mar… Rüdiger von Kummer[1… Richard I Lindley[17], Jea… Peter AG Sandercock[2… Nils Wahlgren[23], Joann… Gregory del Zoppo[24] a… Stroke Thrombolysis T…

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Table 1. Contraindications to alteplase treatment for stroke in FDA and EMA approved product inserts and AHA and ESO guidelines.

	FDA[8]	EMA[9]	AHA acute stroke guideline 2013[10]	ESO acute stroke guideline 2008, 2009[11]
Delay to treatment	>3 h	>4.5 h	>4.5 h	>4.5 h
Age boundaries	Caution advanced age[a]	<18, >80 excluded	<18 yrs excluded; >80 yrs excluded 3–4.5 h	–
Stroke severity (NIHSS)	–	Minor neurological deficit or NIHSS >25	none <3 h; >25 3–4.5 h	–
Blood pressure at treatment	Severe hypertension: caution SBP >175 mmHg or DBP >110 mmHg[a]	SBP >185 mmHg, DBP >110 mmHg or aggressive management necessary to reduce BP to these limits	SBP >185 mmHg or DBP >110 mmHg	SBP >185 mmHg
Prior stroke and diabetes	–	Yes	No <3 h; Yes 3–4.5 h	–
INR if on coumarin/warfarin sodium	>1.7	>1.3	>1.7 <3 h; any anticoagulant 3–4.5 h	–
Stroke <3 months	–[a]	Yes	Yes	–
Aneurysms, neoplasm, arterial/venous malformation	Yes	Yes	Yes	–
Intracranial surgery	<3 months	Ever	Recent	–
Seizure at onset	–	Yes	Yes (with postictal residual impairment)	–
Blood glucose	–	<50 or >400 mg/dL	<50 mg/dL	–
Heparin <48 h	Monitor	Yes	Yes	–
Platelets	–	<100,000/mm^3	<100,000/mm^3	–
Prior ICH	–	Yes	Yes	–
Extensive ischemic change or mass effect	–	–	Yes	–

AHA: American Heart Association; DBP: diastolic blood pressure; EMA: European Medicines Agency; ESO: European Stroke Organisation; FDA: Food and Drug Administration; SBP: systolic blood pressure; ICH: Intracerebral haemorrhage; NIHSS: National Institutes of Health Stroke Scale.
[a]States "the risks of bleeding are increased and should be weighed against the benefits", not contraindication.

…ent of acute ischemic …ited States marketing …n upper age limit or …ed trials of intravenous …come (modified Rankin …emorrhage, and 90-day … patients who met the …1.42, 95% CI 1.21–1.68 …). By 90 days, there was …25 and 1.01, 0.86–1.19, …rly, alteplase increased … US approval and 3326 …vely), but not for those …ed for the current and …ut mortality remained … …uld each increase the number of patients deriving net benefit from alteplase by 90 days after acute ischemic stroke, without excess mortality.

Hacke, Stroke 2016

Trombolisi sistemica: criteri assoluti di esclusione

- ✓ Emorragia intracranica alla TAC cerebrale
- ✓ Sospetto clinico di ESA, anche se TAC normale
- ✓ Somministrazione di eparina endovena nelle precedenti 48 ore e aPTT eccedente limite normale superiore del laboratorio
- ✓ Conta piastrinica < 100.000/mm3
- ✓ Diatesi emorragica nota
- ✓ Sanguinamento grave in atto o recente
- ✓ Sospetto di emorragia intracranica in atto
- ✓ Endocardite batterica, pericardite
- ✓ Pancreatite acuta
- ✓ Neoplasia con aumentato rischio emorragico
- ✓ Grave epatopatia, compresa insufficienza epatica, cirrosi, ipertensione portale
- ✓ (varici esofagee), epatite attiva
- ✓ Retinopatia emorragica, es in diabetici alterazioni del visus
- ✓ Alto rischio emorragico per comorbidità
- ✓ Recenti (< 10 giorni) massaggio cardiaco esterno traumatico, parto, puntura di
- ✓ vaso sanguigno non comprimibile (es. vena succlavia o giugulare)
- ✓ Malattia ulcerosa del tratto gastroenterico (<3mesi)

Trombolisi sistemica: criteri relativi di esclusione

- ✓Insorgenza dell'ictus > 4.5 ore
- ✓Ictus grave clinicamente (es. NIHSS >25) e/o sulla base di adeguate tecniche di neuroimmagini
- ✓Deficit lieve o rapido miglioramento dei sintomi (30 minuti)
- ✓Ora di insorgenza non nota o ictus presente al risveglio
- ✓Crisi convulsiva all'esordio dell'ictus
- ✓Paziente con storia di ictus e diabete concomitante
- ✓Glicemia < 50 o > 400 mg/dl
- ✓Pregresso ictus negli ultimi 3 mesi
- ✓Ipertensione arteriosa grave non controllata
- ✓Paziente in terapia anticoagulante orale
- ✓Paziente in terapia anticoagulante con eparine a basso peso molecolare
- ✓Storia di patologie del SNC: neoplasia, intervento chirurgico cerebrale o midollare, aneurisma
- ✓Aneurisma arterioso, malformazione artero-venosa
- ✓Storia di emorragia intracranica (parenchimale o subarcnoidea)
- ✓Stato di gravidanza
- ✓Intervento chirurgico maggiore o grave trauma (< 3 mesi)

✓ Ictus gra … di
neuroimm…

IV thrombolysis in very severe and severe ischemic stroke

Results from the SITS-ISTR Registry

Michael V. Mazya, MD, PhD
Kennedy R. Lees, MD, FRCP
David Collas, BSc, MBBS, FRCP
Viiu-Marika Rand, MD
Robert Mikulik, MD, PhD
Danilo Toni, MD, PhD
Nils Wahlgren, MD, PhD
Niaz Ahmed, MD, PhD

Correspondence to Dr. Mazya: michael.mazya@karolinska.se

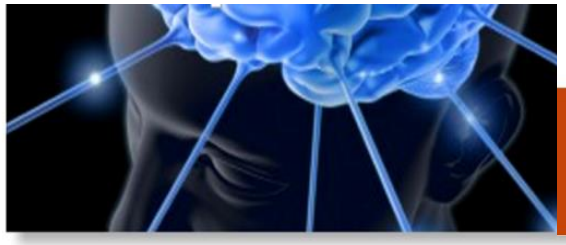
ABSTRACT

Objective: To study the safety of off-label IV thrombolysis in patients with very severe stroke (NIH Stroke Scale [NIHSS] scores >25) compared with severe stroke (NIHSS scores 15-25), where treatment is within European regulations.

Methods: Data were analyzed from 57,247 patients with acute ischemic stroke receiving IV tissue plasminogen activator in 793 hospitals participating in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Registry (2002-2013). Eight hundred sixty-eight patients (1.5%) had NIHSS scores >25 and 19,995 (34.9%) had NIHSS scores 15-25. Outcome measures were parenchymal hemorrhage, symptomatic intracerebral hemorrhage, mortality, and functional outcome.

Results: Parenchymal hemorrhage occurred in 10.7% vs 11.0% ($p = 0.79$), symptomatic intracerebral hemorrhage per SITS-MOST (SITS-Monitoring Study) in 1.4% vs 2.5% ($p = 0.052$), death at 3 months in 50.4% vs 26.9% ($p < 0.001$), and functional independence at 3 months in 14.0% vs 29.0% ($p < 0.001$) of patients with NIHSS scores >25 and NIHSS scores 15-25, respectively. Multivariate adjustment did not change findings from univariate comparisons. Posterior circulation stroke was more common in patients with NIHSS scores >25 (36.2% vs 7.4%, $p < 0.001$), who were also more often obtunded or comatose on presentation (58.4% vs 7.1%, $p < 0.001$). Of patients with NIHSS scores >25, 26.2% were treated >3 hours from symptom onset vs 14.5% with NIHSS scores of 15-25.

Conclusions: Our data show no excess risk of cerebral hemorrhage in patients with NIHSS score >25 compared to score 15-25, suggesting that the European contraindication to IV tissue plasminogen activator treatment at NIHSS levels >25 may be unwarranted. Increased mortality and lower rates of functional independence in patients with NIHSS score >25 are explained by higher stroke severity, impaired consciousness on presentation due to posterior circulation ischemia, and longer treatment delays. *Neurology*® 2015;85:2098-2106



II MEETING DELLE NEUROSCIENZE TOSCANE

Società dei Neurologi, Neurochirurghi e Neuroradiologi Ospedalieri

Sin

DALLE SINDROMI ALLE MALATTIE NEUROLOGICHE: RICERCA TRASLAZIONALE, APPROPRIATEZZA DIAGNOSTICA E TERAPEUTICA

6-7-8 APRILE 2018 FIRENZE

CENTRO DIDATTICO MORGAGNI
Viale Giovan Battista Morgagni 40, Firenze

ISO
ITALIAN STROKE ORGANIZATION

Raccomandazioni

Il trattamento con r-tPA e.v. ng, il 10% della dose in bolo, il rimanente in infusio azienti con:

✓deficit lieve o in rapido mi le al momento di iniziare il trattamento fo **Grado B**

Up to 25% of patients excluded d neurological deficit may later deteriorate with unfavora
Rapid improvement should be r from treatment only if it leads to a NIHSS score of 0

- Seizure-like rytmic jerking da i silare)
- Capsular warning syndrome: s *K, 2014]*
- Pontine warning syndrome *[D*

Task Force Consensus: Definition and Clinical Context of Rapidly Improving Stroke Symptoms as an Exclusion Criterion for Intravenous Alteplase

Ictus in rapido miglioramento
I seguenti sintomi possono essere considerati disabilitanti:

Emianopsia completa(≥2 su NIHSS item 3) o afasia severa (≥2 su NIHSS item 9) o estinzione visiva o sensoriale (≥1 su NIHSS item 11)

Ogni ipostenia limitante lo sforzo sostenuto contro gravità (≥2 su NIHSS item 6 o 7)

Ogni deficit con NIHSS score >5

Ogni deficit residuo considerato potenzialmente disabilitante dal paziente.

Stroke. 2013;44:2500–2505.

Raccoman

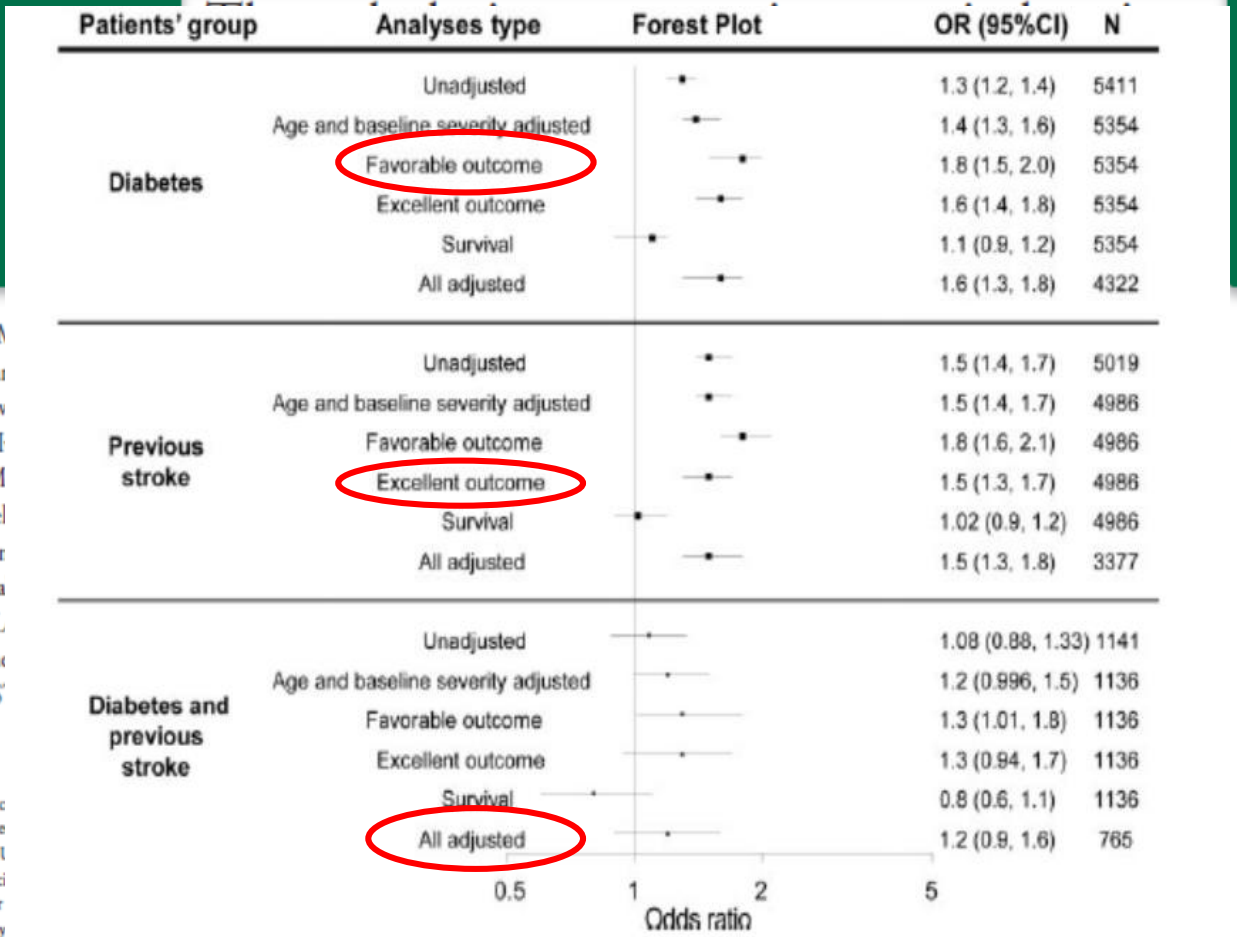
Il trattame … dose in bolo, il rir…

✓deficit li… di iniziare il trattam…

…ado B

✓storia di…

…ado B



(A) Forest plot showing outcomes for various analyses in unaffected patients' population. Unadjusted and age- and baseline-adjusted analyses refer to ordinal regression analysis. Odds refer to common odds for improved outcomes at each Rankin category. Favorable outcomes refer to Rankin 0-2 whereas excellent outcomes refer to Rankin 0-1. All adjusted analysis refers to an adjusted analysis in which adjustment were made for all variables that differed at baseline. (B) Forest plot showing outcomes for various analyses in affected patients' population. Unadjusted and age- and baseline-adjusted analyses refers to ordinal regression analysis. Odds ratio refers to common odds for improved outcomes at each Rankin category. Favorable outcomes refer to Rankin 0-2 whereas excellent outcomes refer to Rankin 0-1. All adjusted analysis refers to an adjusted analysis in which adjustment was made for all variables that differed at baseline. CI = confidence interval; OR = odds ratio.

Raccomandazioni

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 indicato** in pazienti con:

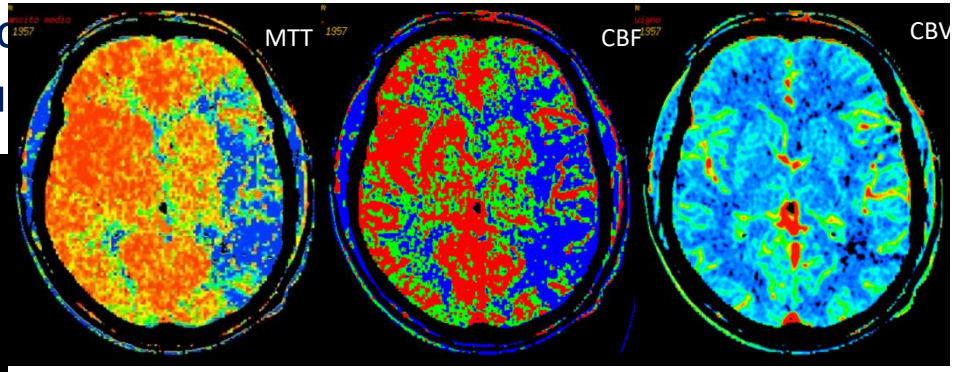
✓deficit lieve o in rapido miglioramento ma ancora rilevabile al momento di iniziare il trattamento — **Forte a favore** — **Grado B**

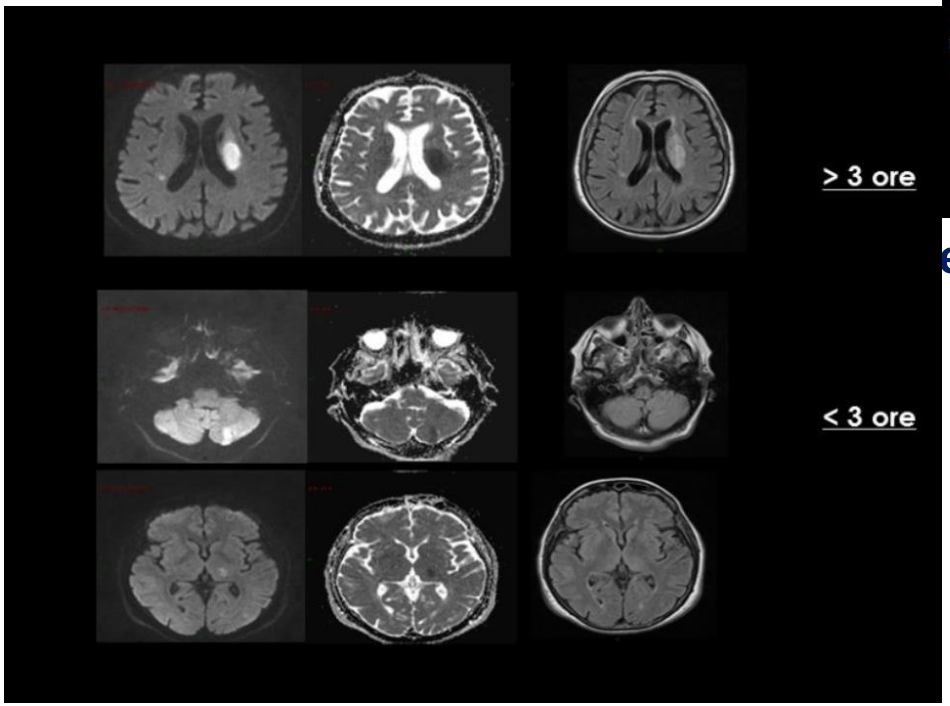
✓storia di pregresso ictus e diabete — **Forte a favore** — **Grado B**

✓ora di insorgenza dell' ictus non nota o ictus presente 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 MR DW con MR FLAIR) — **Debole a favore** — **Grado D**

Raccomandazioni

Il trattamento con r-tPA e.v. (0,9 mg/kg, do
bolo, il rimanente in infusione di 60 minu





e a favore **Grado D**

RACCOMANDAZIONI AHA/ASA

Trombolisi **non raccomandata nell'ictus al risveglio se ultima osservazione >4.5 h**
Classe III, Livello evidenza B

Non è raccomandato **l'uso delle immagini (al di fuori dei trials)** per chiarire un onset indeterminato
Classe III, Livello evidenza B

Raccomandaz

Il trattamento … a dose in bolo, il riman…

✓ora di insorg… …ora le neuroimmag… …mismatch tessutale e/o… …nfronto MR DW con MR …

Stroke

Journal of the American Heart Association

American Heart Association | American Stroke Association

Stroke With Unknown Time of Symptom Onset: Baseline Clinical and Magnetic Resonance Imaging Data of the First Thousand Patients in WAKE-UP

Götz Thomalla, Florent Boutitie, Jochen B. Fiebach, Claus Z. Simonsen, Norbert Nighoghossian, Salvador Pedraza, Robin Lemmens, Pascal Roy, Keith W. Muir, Martin Ebinger, Ian Ford, Bastian Cheng, Ivana Galinovic, Tae-Hee Cho, Josep Puig, Vincent Thijs, Matthias Endres, Jens Fiehler and Christian Gerloff

Stroke. published online February 7, 2017;

WAKE-UP TRIAL (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke: A Randomized, Doubleblind, Placebo-Controlled Trial)

Sintesi 9.1

Serie cliniche hanno riportato sicurezza ed efficacia della trombolisi e.v. in pazienti con ictus al risveglio selezionati in base a presenza ed estensione dei segni precoci di infarto alla TC.

Raccomandazioni

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 indicato** in pazienti con:

✓deficit lieve o in rapido miglioramento ma ancora rilevabile al momento di iniziare il trattamento — **Forte a favore** — **Grado B**

✓storia di pregresso ictus e diabete — **Forte a favore** — **Grado B**

✓ora di insorgenza dell' ictus non nota o ictus presente 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 MR DW con MR FLAIR) — **Debole a favore** — **Grado D**

✓ TAO con farmaci aVK ed INR ≤ 1.7 — **Debole a favore** — **Grado D**

Safety of Intravenous Thrombolysis for Ischemic Stroke in Patients Treated with Warfarin

Michael V. Mazya, MD,[1] Kennedy R. Lees, MD, FRCP,[2] Romesh M
FRACP,[3] Risto O. Roine, MD, PhD,[4] Raymond C. S. Seet, MD,
Nils Wahlgren, MD, PhD,[1] and Niaz Ahmed, MD, PhD,[1] for t
Implementation of Thrombolysis in Stroke Investigators

RACCOMANDAZIONI AHA/ASA Scientific Statement

- La trombolisi può essere ragionevole in pazienti in TAO con INR<1.7 (Classe IIb; Liv B)
- In pazienti in TAO con INR>1.7 la trombolisi non è raccomandata (Classe III; Liv B)

Outcome measure	W (N=768) vs non-W (N=44306) aO.R. (95% C.I.)*	
SICH per SITS-MOST	1.23 (0.72-2.11)	p = 0.46
Mortality	1.05 (0.83-1.35)	p = 0.66
mRS 0-2	1.01 (0.81-1.24)	p = 0.96

*aOR: adjusted for age, stroke severity and co-morbidities

Mazya MV, Ann Neurol 2013

european journal of neurology
the official journal of the european academy of neurology

Eur J Neurol. 2018 Jan 23. doi: 10.1111/ene.13582. [Epub ahead of print]

forward 20 1997/2017

SPREAD
Stroke Prevention And Educational Awareness Diffusion

VIII Edizione
Ictus cerebrale:

Intravenous thrombolysis for acute ischaemic stroke in patients on direct oral anticoagulants.

Touzé E[1], Gruel Y[2], Gouin-Thibault I[3], De Maistre E[4], Susen S[5], Sie P[6], Derex L[7].

Author information

Abstract

BACKGROUND AND PURPOSE: Whereas intravenous thrombolysis (IVT) is allowed for acute ischaemic stroke in patients on vitamin K antagonists with international normalized ratio ≤1.7, there are no similar recommendations for patients on direct oral anticoagulants (DOACs), notably due to the lack of coagulation tests to assess the therapeutic effects. Although the literature is scarce, consisting of small case series and retrospective studies, considering the frequency of this situation the French Vascular Neurology Society and the French Study Group on Haemostasis and Thrombosis have worked on a joint position paper to provide a practical position regarding the emergency management of ischaemic stroke in patients on DOACs.

METHOD: Based on a review of the literature, the authors wrote a first text that was submitted to a broad panel of members from the two societies. The text was then amended by the authors to address experts' comments and to reach a consensus.

RESULTS: In patients with normal renal function and who stopped the DOAC for at least 48 h, the management should not differ from that in patients without oral anticoagulant. In patients who are still on DOACs, mechanical thrombectomy is encouraged preferentially when applicable in first line. Otherwise, when specific tests are available, values <50 ng/ml indicate that IVT is allowed. In the absence of specific tests, standard tests (thrombin time, prothrombin time and activated partial thromboplastin time) can be used for dabigatran and rivaroxaban, although interpretation of these tests may be less reliable. In some patients on dabigatran, idarucizumab may be used before IVT.

CONCLUSIONS: In this expert opinion paper, it is suggested that IVT can be performed in patients selected according to the time elapsed since the drug was last taken, renal function, type of hospital where the patient is admitted and plasma concentration of DOAC.

Raccomandazioni GPP

- ✓ In pazienti con deficit neurologico focale esordito con crisi epilettica, il Gruppo ISOSPREAD suggerisce il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi quando ci siano evidenze cliniche, eventualmente supportate con neuroimmagini, che il deficit neurologico residuo non è un deficit post-critico ma sia attribuibile ad ischemia cerebrale.
- ✓ In pazienti con glicemia <50 mg/dl e deficit neurologico che permane invariato anche dopo il ripristino di una glicemia normale, il Gruppo ISO-SPREAD suggerisce il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi.
- ✓In pazienti con glicemia >400 mg/dl che, trattata con insulina rapida s.c. o in infusione e.v. scende sotto i 200 mg/dl, il Gruppo ISO-SPREAD suggerisce il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi.

Raccomandazioni GPP

✓ In pazienti con ipertensione arteriosa grave, il Gruppo ISO-SPREAD suggerisce il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi una volta raggiunto il range pressorio PAS <185 e PAD <110, che dovrà essere mantenuto anche nelle 24 ore successive alla terapia trombolitica.

✓ In pazienti con pregresso ictus negli ultimi 3 mesi il Gruppo ISO-SPREAD suggerisce il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi, tenendo in considerazione:

- estensione della lesione e intervallo temporale dal primo ictus (rischio di emorragia maggiore per lesioni più estese e più recenti);
- età del paziente (rischio di emorragia potenzialmente maggiore con età più avanzata e rapporto rischio/beneficio in funzione dell'aspettativa di vita);
- gravità potenziale del nuovo evento (definibile anche con tecniche di neuroimmagini come MR DW/PW o pTC).

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

American Heart Association | American Stroke Association

life is why™

Age Diabetes mellitus Prior stroke Severity OACs Imaging	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory.† (*Class I; LOE B-R*)‡
Urgency	Treatment should be initiated as quickly as possible within the above listed time frames because time to treatment is strongly associated with outcomes.† (*Class I; LOE A*)
BP	IV alteplase is recommended in patients whose BP can be lowered safely (to <185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.† (*Class I; LOE B-NR*)‡
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† (*Class I; LOE A*)
CT	IV alteplase administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity).† (*Class I; LOE A*)
Prior antiplatelet therapy	IV alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH.† (*Class I; LOE A*)
	IV alteplase is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH.† (*Class I; LOE B-NR*)‡
End-stage renal disease	In patients with end-stage renal disease on hemodialysis and normal aPTT, IV alteplase is recommended.† (*Class I; LOE C-LD*)‡ However, those with elevated aPTT may have elevated risk for hemorrhagic complications.

Stroke

Firenze – 7 Aprile 2018

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

American Heart Association | American Stroke Association

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4. In otherwise eligible patients who have had a previously demonstrated small number (1–10) of CMBs on MRI, administration of IV alteplase is reasonable.	IIa	B-NR	New recommendation.
5. In otherwise eligible patients who have had a previously demonstrated high burden of CMBs (>10) on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit.	IIb	B-NR	New recommendation.

9. The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making.	I	C-EO	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
10. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.	IIa	B-NR	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

3.7. Mechanical Thrombectomy	COR	LOE	New, Revised, or Unchanged
1. Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.
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.

Sintesi

- Ictus al risveglio selezionati in base alla presenza ed estensione dei segni precoci di infarto alla TC
- Segni precoci di lesione visibili alla TC
- Pazienti trattati con farmaci anticoagulanti diretti

American Journal of Emergency Medicine (2013) **31**, 448.e1–448.e3

ELSEVIER

Case Report

Systemic thrombolysis for stroke in pregnancy

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

- Aneurismi cerebrali non rotti
- Storia di emorragia intracranica (parenchimale o ESA)
- Pazienti in gravidanza
- Pazienti con mestruazione
- Pazienti con recente (<14 giorni secondo le linee guida AHA, <3 mesi secondo la licenza EMA) intervento chirurgico maggiore o trauma maggiore non cranico

PDTA AREA VASTA CENTRO

Direttore per la Programmazione Area Vasta Centro
Dr. Rocco Donato Damone

Referenti Rete ICTUS Area Vasta Centro :
Prof Domenico Inzitari, Dott .Pasquale Palumbo, Dott Lucia Turco, Dott. P. D'Onofrio

CRITERIO	INCLUSIONE	ESCLUSIONE RELATIVA	ESCLUSIONE ASSOLUTA
Età	≥ 18	età <18 anni, considerare la possibilità di effettuare la trombolisi e.v., tenendo conto del rapporto rischio-beneficio e della prognosi in assenza di trattamento	> 80 aa se insorgenza dei sintomi > 3 ore o tempo di insorgenza non noto e potenzialmente superiore alle 3 ore
Durata sintomo	>30'		< 30'
NIHSS	Deficit misurabile del linguaggio, motorio , cognitivo, di sguardo, del visus e/o di neglect		
Esordio sintomi	< 4.5 ore (≤ 3 ore per età >80aa)	non noto o ictus al risveglio se neuroimmagini avanzate definiscono una zona di mismatch tessutale e/o consentono di datare l'evento almeno entro le 3 ore	>4.5 ore (>3 ore per età >80 aa)

The START nomogram for individualized prediction of the probability of unfavorable outcome after intravenous thrombolysis for stroke

Manuel Cappellari[1], Gianni Turcato[2], Stefano Forlivesi[1], Fabio Bagante[3], Gianfranco Cervellin[4], Giuseppe Lippi[5], Bruno Bonetti[1], Paolo Bovi[1] and Danilo Toni[6]

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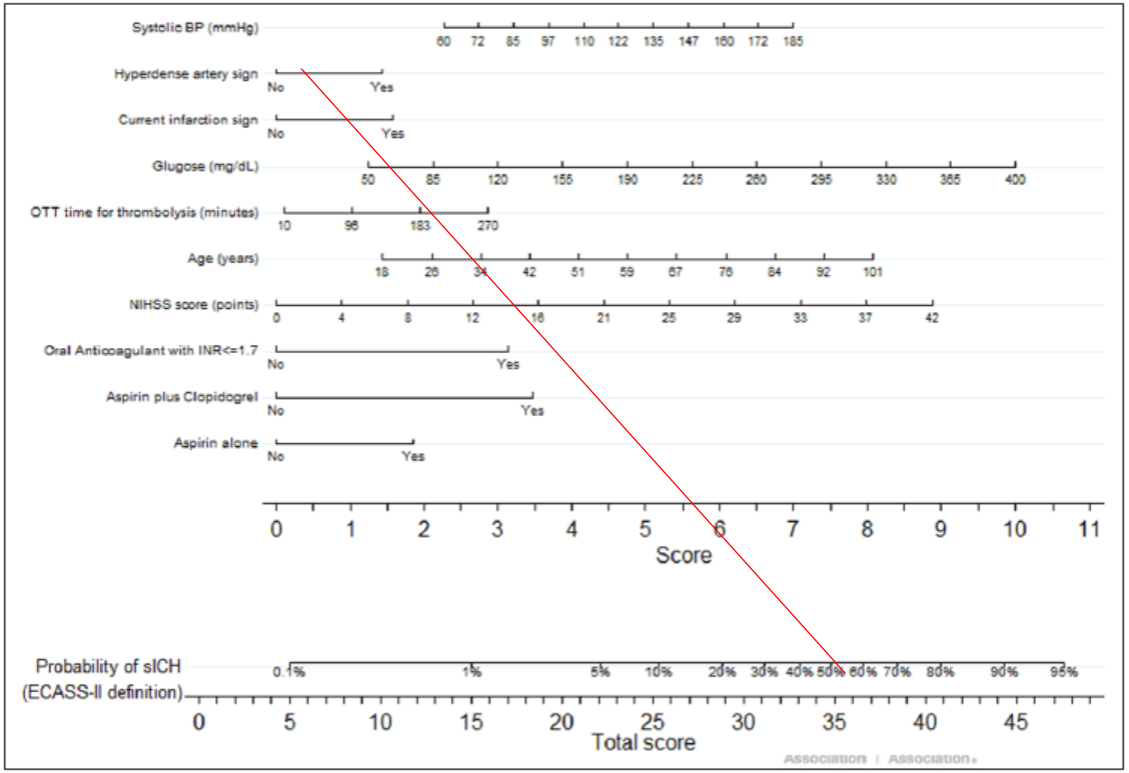
SAGE

Figure 1. START nomogram for predicting the probability of three-month unfavorable outcome in patients receiving intravenous thrombolysis. NIHSS: NIH Stroke Scale; OTT: onset-to-treatment.



Cappellari M, Journal of Stroke 2018

In conclusione:

- L'ampliamento della finestra terapeutica non deve far aumentare i tempi critici di trattamento, ricordando che l'efficacia del trattamento è maggiore quanto più precoce
- Essere confidenti del fatto che la mortalità non sembra incrementata dal trattamento trombolitico
- Tenere a mente le Linee Guida, valutando caso per caso

Grazie per l'attenzione

Firenze – 7 Aprile 2018