Le nuove raccomandazioni e sintesi dello SPREAD 2016

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Barletta

The New England
Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

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

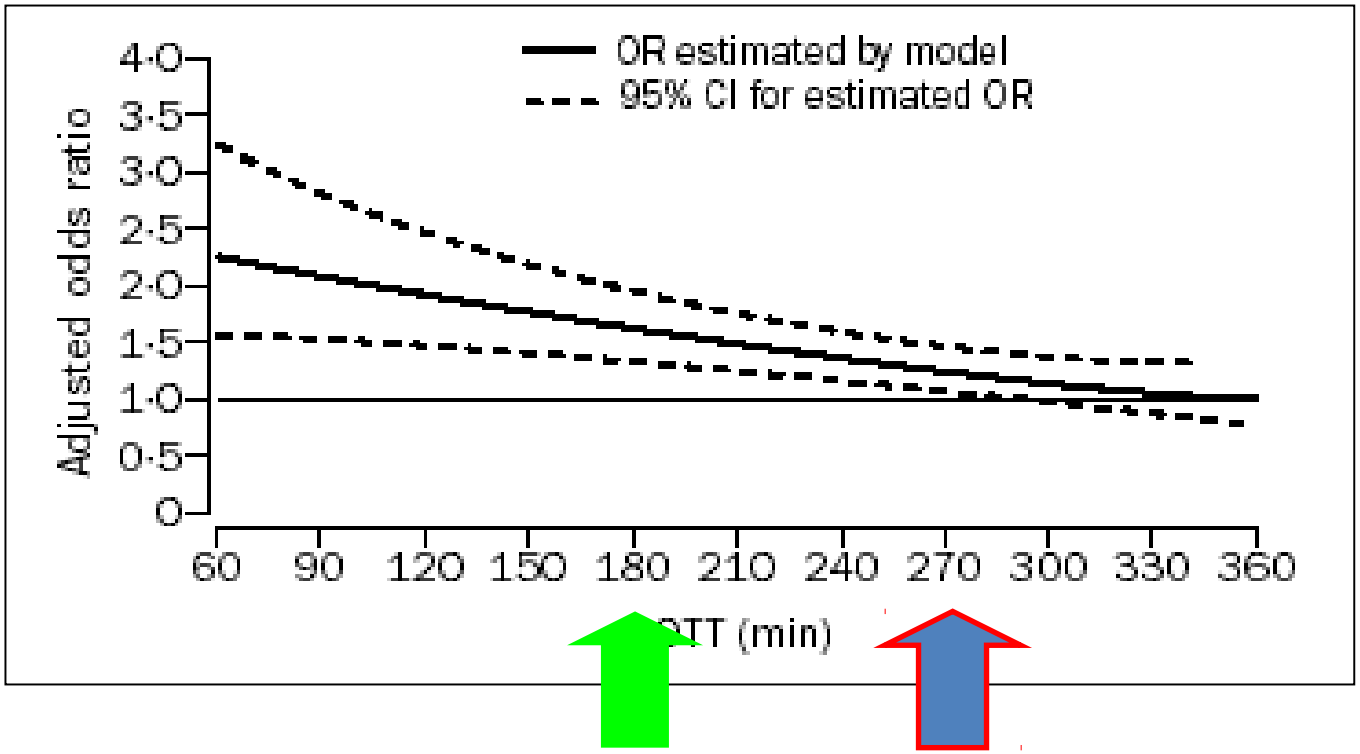
Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic 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.)

Trombolisi endovenosa con rt-PA



OR per esito favorevole a 3 mesi nei pazienti trattati con rt-PA rispetto ai controlli

The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Lancet 2004; 363: 768–774.

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*

Table 1. Major Inclusion and Exclusion Criteria.

Main inclusion criteria
Acute ischemic stroke
Age, 18 to 80 years
Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration
Stroke symptoms present for at least 30 minutes with no significant improvement before treatment
Main exclusion criteria
Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000 per cubic millimeter
Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

ECASS Study NEJM, 2008

In this study, intravenous alteplase given 3 to 4.5 hours (median, 3 hours 59 minutes) after the onset of stroke symptoms was associated with a modest but significant improvement in the clinical outcome, without a higher rate of symptomatic intracranial hemorrhage than that reported previously among patients treated within 3 hours.

Although our findings suggest that treatment with alteplase may be effective in patients who present 3 to 4.5 hours after the onset of stroke symptoms, patients should be treated with alteplase as early as possible to maximize the benefit. Having more time does not mean we should be allowed to take more time.

ECASS Study 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**

- Studio pragmatico, multicentrico, randomizzato, controllato, aperto
- Elegibilità basata sul criterio di incertezza
- Trombolisi eseguibile entro 6 ore
- Pazienti arruolabili senza limiti superiori di età

Lancet 2012

Cosa ci dice l'IST 3

- I pazienti vanno comunque trattati il più presto possibile
- E' giusto trattare i pazienti > 80 anni ed indipendentemente dalla gravità
- Trattare i pazienti entro le 4.5 ore dall'esordio non comporta ulteriori rischi ed offre tendenzialmente vantaggi sull'outcome a sei mesi

Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis

Joanna M Wardlaw, Veronica Murray, Eivind Berge, Gregory del Zoppo, Peter Sandercock, Richard L Lindley, Geoff Cohen

Lancet 2012

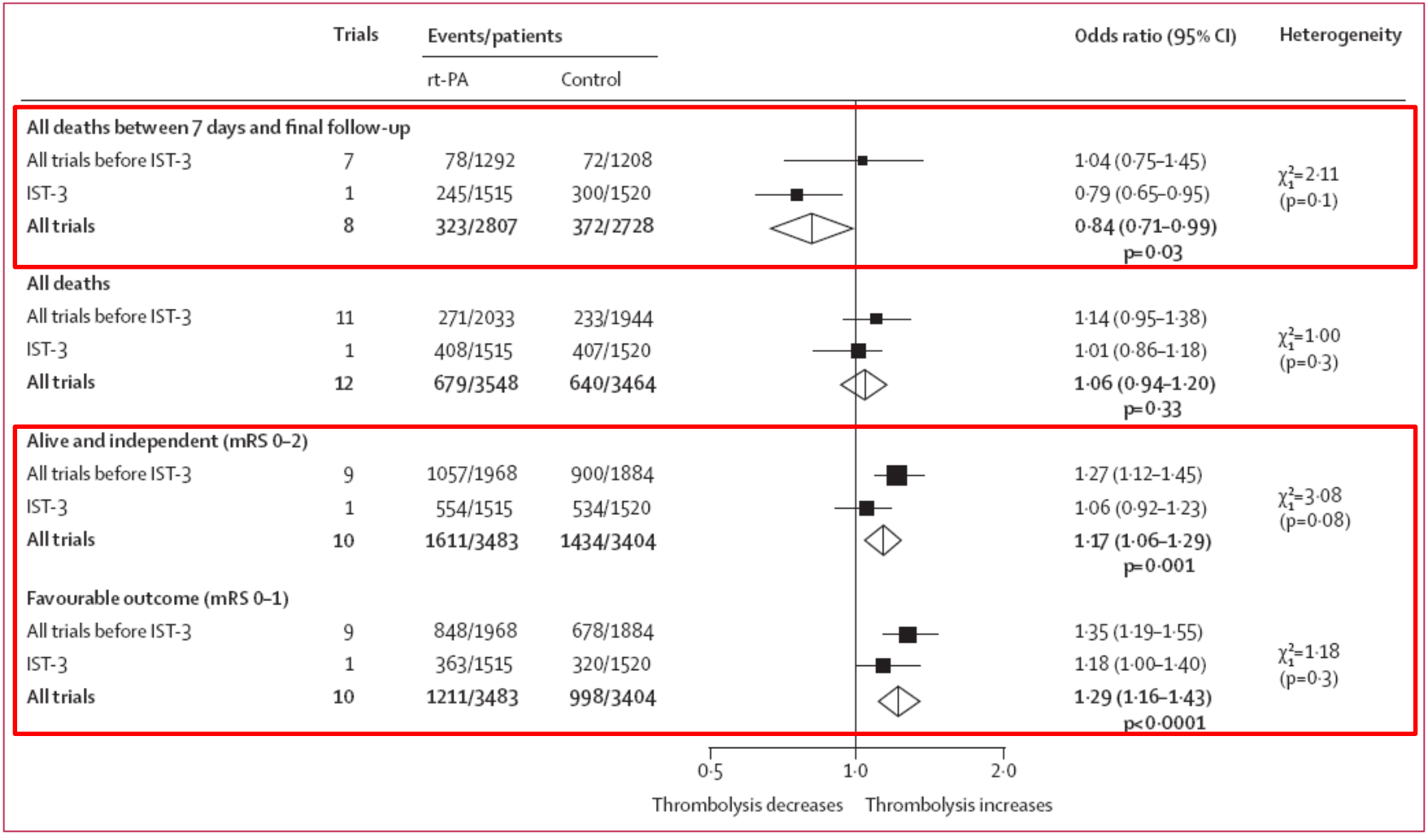


Figure 2: Effects of rt-PA on outcomes at final follow-up

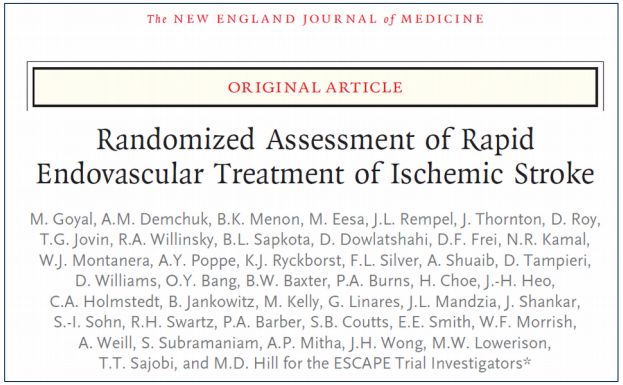
Germans Trias i Pujol
Hospital
Unitat d'ictus


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

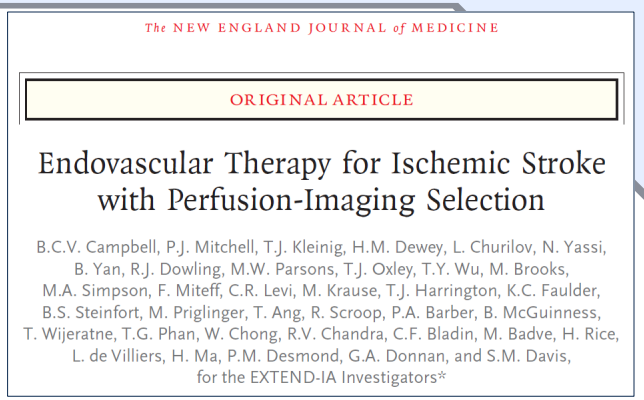
O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

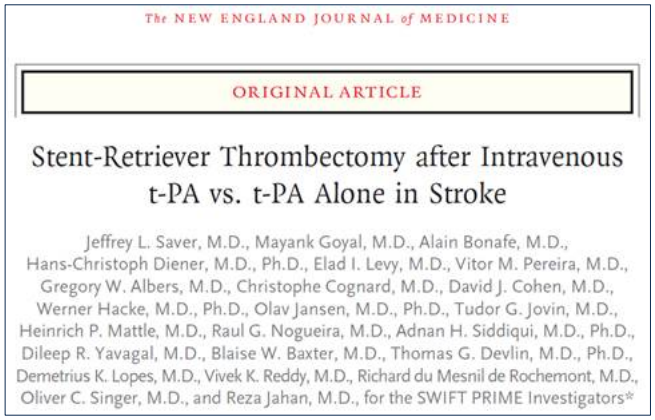
M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, W.J. Montanera, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tampieri, D. Williams, O.Y. Bang, B.W. Baxter, P.A. Burns, H. Choe, J.-H. Heo, C.A. Holmstedt, B. Jankowitz, M. Kelly, G. Linares, J.L. Mandzia, J. Shankar, S.-I. Sohn, R.H. Swartz, P.A. Barber, S.B. Coutts, E.E. Smith, W.F. Morrish, A. Weill, S. Subramaniam, A.P. Mitha, J.H. Wong, M.W. Lowerison, T.T. Sajobi, and M.D. Hill for the ESCAPE Trial Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

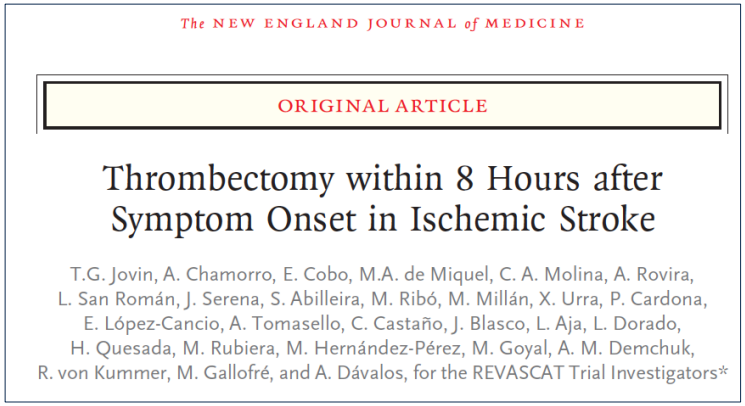
B.C.V. Campbell, P.J. Mitchell, T.J. Kleinig, H.M. Dewey, L. Churilov, N. Yassi, B. Yan, R.J. Dowling, M.W. Parsons, T.J. Oxley, T.Y. Wu, M. Brooks, M.A. Simpson, F. Miteff, C.R. Levi, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, M. Priglinger, T. Ang, R. Scroop, P.A. Barber, B. McGuinness, T. Wijeratne, T.G. Phan, W. Chong, R.V. Chandra, C.F. Bladin, M. Badve, H. Rice, L. de Villiers, H. Ma, P.M. Desmond, G.A. Donnan, and S.M. Davis, for the EXTEND-IA Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C. A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A. M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*

Berkhemer et al. NEJM 2015;372:11-20
Goyal et al. NEJM 2015;372:1019-1030
Saver et al. NEJM 2015;372:2285-2295
Campbell BCV et al. NEJ M 2015;372:1009-1018
Jovin et al. NEJM 2015;372:2296-2306

Cosa ci dicono le linee guida

1. Linee guida e trombolisi venosa
2. Linee guida e trombectomia meccanica
3. Linee guida e organizzazione dei servizi

Cosa ci dicono le linee guida

1. Linee guida e trombolisi venosa

EUROPEAN STROKE ORGANISATION

Guidelines for Management of Ischaemic Stroke 2008

Original Guidelines 2008

Slidekit 2008

Update Guidelines January 2009 New Elements

The ESO Guidelines have been updated with regard to thrombolytic therapy. The modifications were discussed and prepared at the Karolinska Stroke Update Meeting, November 2008, and have been approved by the ESO Guideline Committee and the ESO Executive Committee. The updates to the guidelines are as follows:

ESO Guideline Update (Abstract) – January 2009

ESO Guideline Update – January 2009

http://www.eso-stroke.org/

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Edward C. Jauch, Jeffrey L. Saver, Harold P. Adams, Jr, Askiel Bruno, J.J. (Buddy) Connors, Bart M. Demaerschalk, Pooja Khatri, Paul W. McMullan, Jr, Adnan I. Qureshi, Kenneth Rosenfield, Phillip A. Scott, Debbie R. Summers, David Z. Wang, Max Wintermark and Howard Yonas

on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology

Stroke. 2013;44:870-947; originally published online January 31, 2013;
doi: 10.1161/STR.0b013e318284056a

https://stroke.ahajournals.org/

Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or 1 or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

Jauch et al, Stroke 2013

American Heart Association | American Stroke Association

Table 10. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <3 hours before beginning treatment
- Aged ≥18 years

Exclusion criteria

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to
- Platelet count <100 000/mm^3
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Current use of anticoagulant with INR >1.7 or PT >15 seconds
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative exclusion criteria

Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:

- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy
- Seizure at onset with postictal residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 months)

Jauch et al, Stroke 2013

Table 11. Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative exclusion criteria
Aged >80 years
Severe stroke (NIHSS>25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

Class IIB; Level of Evidence C

Jauch et al, Stroke 2013

American Heart Association | American Stroke Association

forward 20
1997/2017

SPREAD

Stroke Prevention And Educational Awareness Diffusion

VIII Edizione

Ictus cerebrale:

linee guida italiane di prevenzione e trattamento

Raccomandazioni e Sintesi

Stesura del 21 luglio 2016

Linee guida basate sulla metodologia SIGN che consente di utilizzare il giudizio ponderato, ovvero una valutazione della qualità e della importanza degli studi (e non solo della significatività statistica del risultato) e di introdurre le GPP

SIGN The Scottish Intercollegiate Guidelines Network

Gli svantaggi sono chiaramente superiori ai possibili benefici:
Raccomandazione forte a sfavore

Gli svantaggi sono probabilmente superiori ai possibili benefici:
Raccomandazione debole a sfavore

Incertezza nel bilanciamento tra benefici e svantaggi:
Raccomandazione per ulteriore ricerca e possibile raccomandazione condizionale per uso nei trials

I possibili benefici sono probabilmente superiori agli svantaggi:
Raccomandazione debole a favore

I possibili benefici sono chiaramente superiori agli svantaggi:
Raccomandazione forte a favore

Miglior pratica raccomandata sulla base dell'esperienza clinica del gruppo che redige le linee guida:
GPP (Buona Pratica Clinica raccomandata dal gruppo SPREAD)

Raccomandazione 9.1 grado A
Forte a favore

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 entro 4.5 ore dall'esordio di un ictus ischemico senza limiti superiori di età e di gravità

E' comunque indicato che il trattamento sia effettuato il più precocemente possibile

SPREAD
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VIII Edizione

Raccomandazione 9.2 grado B
Forte a favore

Il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi è indicato in pazienti con deficit lieve o in rapido miglioramento ma ancora rilevabile al momento di iniziare il trattamento

Raccomandazione 9.3 grado D
Debole a favore

Il trattamento con r-tPA e.v. è indicato in pazienti con 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)

SPREAD
Stroke Prevention And Educational Awareness Diffusion
VIII Edizione

Raccomandazione 9.4 GPP

In pazienti con deficit neurologico focale esordito con crisi epilettica, il Gruppo ISO-SPREAD 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

Raccomandazione 9.5 **grado B**

Forte a favore

Il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi è indicato in pazienti con storia di pregresso ictus e diabete

Raccomandazione 9.6 GPP

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

SPREAD
Stroke Prevention And Educational Awareness Diffusion
VIII Edizione

Raccomandazione 9.7 GPP

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.

Raccomandazione 9.8 GPP

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).

SPREAD
Stroke Prevention And Educational Awareness Diffusion
VIII Edizione

Raccomandazione 9.9 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.

Raccomandazione 9.10 grado D
Debole a favore

Il trattamento con r-tPA e.v. entro 4.5 ore dall'esordio dei sintomi è indicato in pazienti in terapia anticoagulante orale con farmaci aVK ed INR ≤ 1.7

Raccomandazione 9.14 grado A
Forte contro

In pazienti con ictus ischemico acuto, candidati alla trombolisi per via venosa, non è raccomandato l'uso di trombolitici diversi dal r-tPA.

Raccomandazione 9.18 grado A
Forte contro

In pazienti con ictus ischemico acuto, l'uso degli ultrasuoni per potenziare l' effetto della trombolisi e.v. non è indicato routinariamente

Cosa ci dicono le linee guida

1. Linee guida e trombolisi venosa
2. Linee guida e trombectomia meccanica

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

William J. Powers, Colin P. Derdeyn, José Biller, Christopher S. Coffey, Brian L. Hoh, Edward C. Jauch, Karen C. Johnston, S. Claiborne Johnston, Alexander A. Khalessi, Chelsea S. Kidwell, James F. Meschia, Bruce Ovbiagele and Dileep R. Yavagal
on behalf of the American Heart Association Stroke Council

Stroke. 2015;46:3020-3035; originally published online June 29, 2015;
doi: 10.1161/STR.0000000000000074
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Powers et al. Stroke 2015

1. **Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered *(Class I; Level of Evidence A).*** (Unchanged from the 2013 guideline)

2. **Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria *(Class I; Level of Evidence A).*** (New recommendation):

    a. Prestroke mRS score 0 to 1,

    b. Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,

    c. Causative occlusion of the ICA or proximal MCA (M1),

    d. Age ≥18 years,

    e. NIHSS score of ≥6,

    f. ASPECTS of ≥6, and

    g. Treatment can be initiated (groin puncture) within 6 hours of symptom onset

3. **As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset *(Class I; Level of Evidence B-R).*** (Revised from the 2013 guideline)

4. **When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1) *(Class IIb; Level of Evidence C).* Additional randomized trial data are needed.** (New recommendation)

American Heart Association | American Stroke Association

Powers et al. Stroke 2015

5. **In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable *(Class IIa; Level of Evidence C).* Inadequate data are available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time based or not time based (eg, prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).** (New recommendation)

6. **Although the benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries *(Class IIb; Level of Evidence C).*** (New recommendation)

7. **Endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have demonstrated large-vessel occlusion in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset, but the benefits are not established in this age group *(Class IIb; Level of Evidence C).*** (New recommendation)

8. **Although its benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the ICA or proximal MCA (M1) *(Class IIb; Level of Evidence B-R).* Additional randomized trial data are needed.** (New recommendation)

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forward 20
1997/2017

SPREAD

Stroke Prevention And Educational Awareness Diffusion

VIII Edizione

Ictus cerebrale:

linee guida italiane di prevenzione e trattamento

Raccomandazioni e Sintesi

Stesura del 21 luglio 2016

Raccomandazione 9.11 grado A
Forte contro

In pazienti eleggibili alla trombolisi e.v., trattamenti di riperfusione endoarteriosa non sono raccomandati in alternativa a questa

Raccomandazione 9.12 grado B
Forte a favore

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

Raccomandazione 9.13 GPP

In pazienti con occlusione di arteria vertebrale, basilare o cerebrale posteriore tratto P1, che non rispondono o che non possono essere sottoposti alla trombolisi e.v., il Gruppo ISO-SPREAD suggerisce il ricorso a tecniche di trombectomia meccanica entro 6 ore dall'esordio dei sintomi

SPREAD
Stroke Prevention And Educational Awareness Diffusion
VIII Edizione

Cosa ci dicono le linee guida

1. Linee guida e trombolisi venosa
2. Linee guida e trombectomia meccanica
3. Linee guida e organizzazione dei servizi

Sintesi 8.11

Nella logica di un sistema di servizi in rete, il trasferimento da Ospedale con Unità Neurovascolare (Stroke Unit) di I livello ad Ospedale con Unità Neurovascolare (Stroke Unit) di II livello, deve essere attivato qualora si intenda sottoporre il paziente con ictus acuto al trattamento endovascolare. In questo senso devono essere ottemperati alcuni criteri:

- L'inizio del trattamento endoarterioso (puntura dell'arteria femorale) nella sala angiografica della struttura di II livello dovrebbe avvenire entro e non oltre il tempo massimo di 30 minuti dal termine della trombolisi e.v.
- La procedura di trasferimento deve essere effettuata solo se sono assicurati tempi che consentano l'inizio della procedura endovascolare entro i limiti della finestra terapeutica (in caso contrario la stessa deve essere annullata).
- Il trasporto deve essere effettuato con ambulanza medicalizzata.
- La contemporanea somministrazione di trombolitico e.v. non controindica il trasporto.
- Una volta stabilizzato il paziente può essere reinviato alla Unità Neurovascolare (Stroke Unit di I livello) di provenienza.

Systems of Stroke Care

Powers et al. Stroke 2015

1. **Patients should be transported rapidly to the closest available certified primary stroke center or comprehensive stroke center or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the 2013 guidelines *(Class I; Level of Evidence A)*. In some instances, this may involve air medical transport and hospital bypass.** (Unchanged from the 2013 guideline)

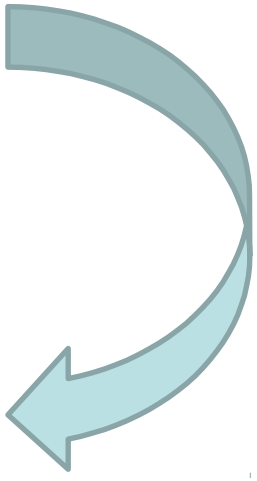
2. **Regional systems of stroke care should be developed. These should consist of the following:**

   a. Healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, such as primary stroke centers, comprehensive stroke centers, and other facilities, and

   b. Centers capable of performing endovascular stroke treatment with comprehensive periprocedural care, including comprehensive stroke centers and other healthcare facilities, to which rapid transport can be arranged when appropriate *(Class I; Level of Evidence A)*. (Revised from the 2013 guideline)

3. **It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for endovascular intervention and to reduce the time to endovascular treatment (*Class IIb; Level of Evidence C*).** (Revised from the 2013 guideline)

4. **Endovascular therapy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified neurointerventionalists. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures *(Class I; Level of Evidence E)*.** (Revised from the 2013 guideline)



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Conclusioni

1. Nessuno dei nuovi risultati relativi alla terapia endovascolare cambia il fatto che i pazienti con sospetto stroke debbano afferire ad un centro di primo livello il più rapidamente possibile per essere trattati con r-tPA endovena, che rimane la terapia di prima linea per l'ictus ischemico acuto.
2. Per tutti i pazienti che posseggono i criteri per la terapia endovascolare, questo trattamento andrebbe preso in considerazione in aggiunta all'r-tPA endovena, trasferendoli immediatamente ad un centro di secondo livello.
3. E' necessario organizzare un sistema assistenziale (quale un modello hub and spoke) per l'ictus ischemico acuto per trasferire il più rapidamente possibile il paziente ad un centro di secondo livello per il trattamento endovascolare.

STROKE
time lost
is
brain lost

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Trombolisi e.v. - Criteri 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

Courtesy of D. Toni

Trombolisi e.v. - Criteri assoluti di esclusione

Insorgenza dell'ictus > 4.5 ore
Emorragia intracranica alla TAC cerebrale
Sospetto clinico di ESA, anche se TC normale
Somministrazione di eparina endovena nelle precedenti 48 ore e aPTT > limite normale superiore
Conta piastrinica < 100.000/mm^3
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 e.v. - Criteri relativi di esclusione

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
Ictus grave clinicamente (es. NIHSS >25) e/o sulla base di adeguate tecniche di neuroimmagini
Paziente in terapia anticoagulante orale (anti-vit.K o anticoagulante diretto)
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)

The guidelines state that patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (class I; level of evidence A):

- Prestroke modified Rankin Scale (mRS) score 0 to 1;
- Acute ischemic stroke with receipt of intravenous recombinant tPA within 4.5 hours of onset;
- Causative occlusion of the internal carotid artery or proximal (M1) middle cerebral artery (MCA);
- Age 18 years or older;
- National Institutes of Health Stroke Scale (NIHSS) score of 6 or greater;
- ASPECT score of 6 or greater;
- Treatment that can be initiated (groin puncture) within 6 hours of symptom onset.

Raccomandazione 9.15 grado A
Forte contro

In pazienti con ictus ischemico acuto, candidati alla trombolisi per via venosa, non è raccomandato l' uso di dosi diverse di r-tPA (rispetto allo standard 0,9 mg/Kg).

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A

- High-quality evidence‡ from more than 1 RCTs
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL E

Consensus of expert opinion based on clinical experience when evidence is insufficient, vague, or conflicting

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C or E does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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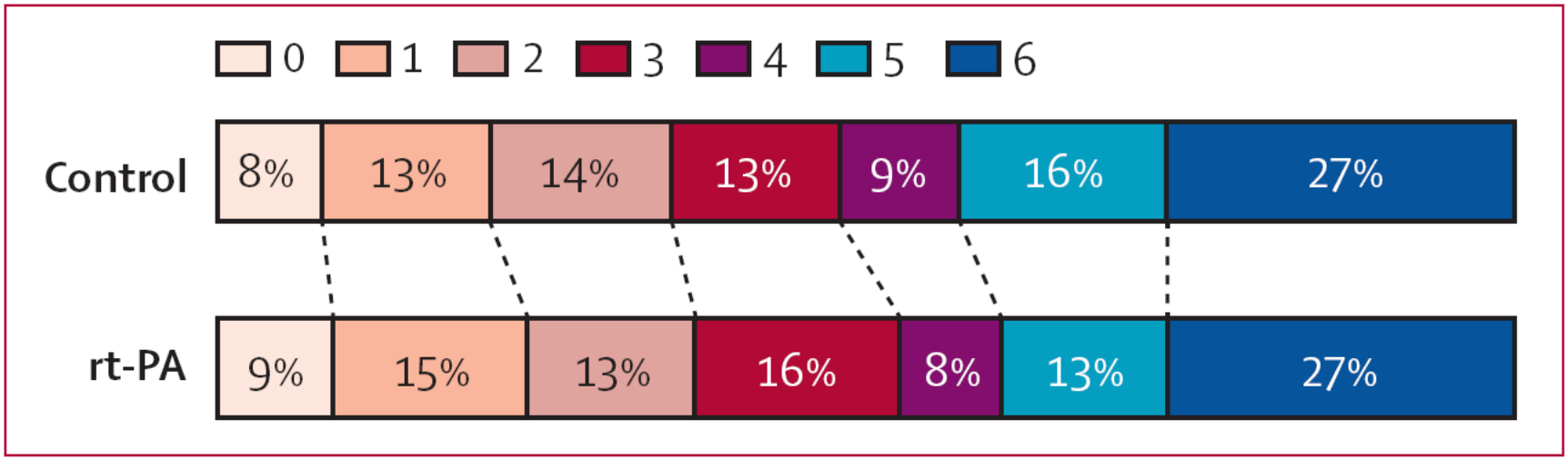
Raccomandazione 5.2e
Forte contro

L’uso routinario di RM o di TC multimodali non è indicato per la selezione di pazienti da sottoporre a trombolisi e.v. entro le 4.5 ore dall’esordio dei sintomi.

IST 3 – outcome a sei mesi



Lancet 2012