Azienda Ospedaliero Universitaria Careggi

60° Congresso Nazionale SIGG – Napoli – Novembre 2015

Nuove strategie nel trattamento dell'ictus acuto: focus sull'anziano

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Ictus cerebrale: dimensioni del problema

2° causa di morte e 1° causa di disabilità

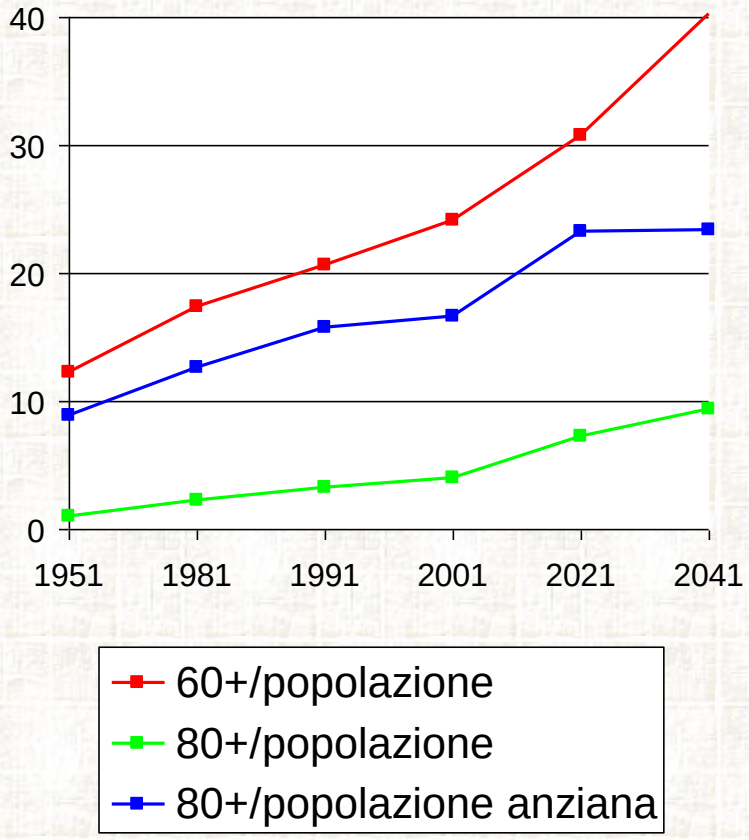
Oltre 200.000 ictus all’anno in Italia tra primi ictus e recidive

Di questi il 20% muore, il 50% rimane disabile

950.000 persone colpite da ictus in Italia

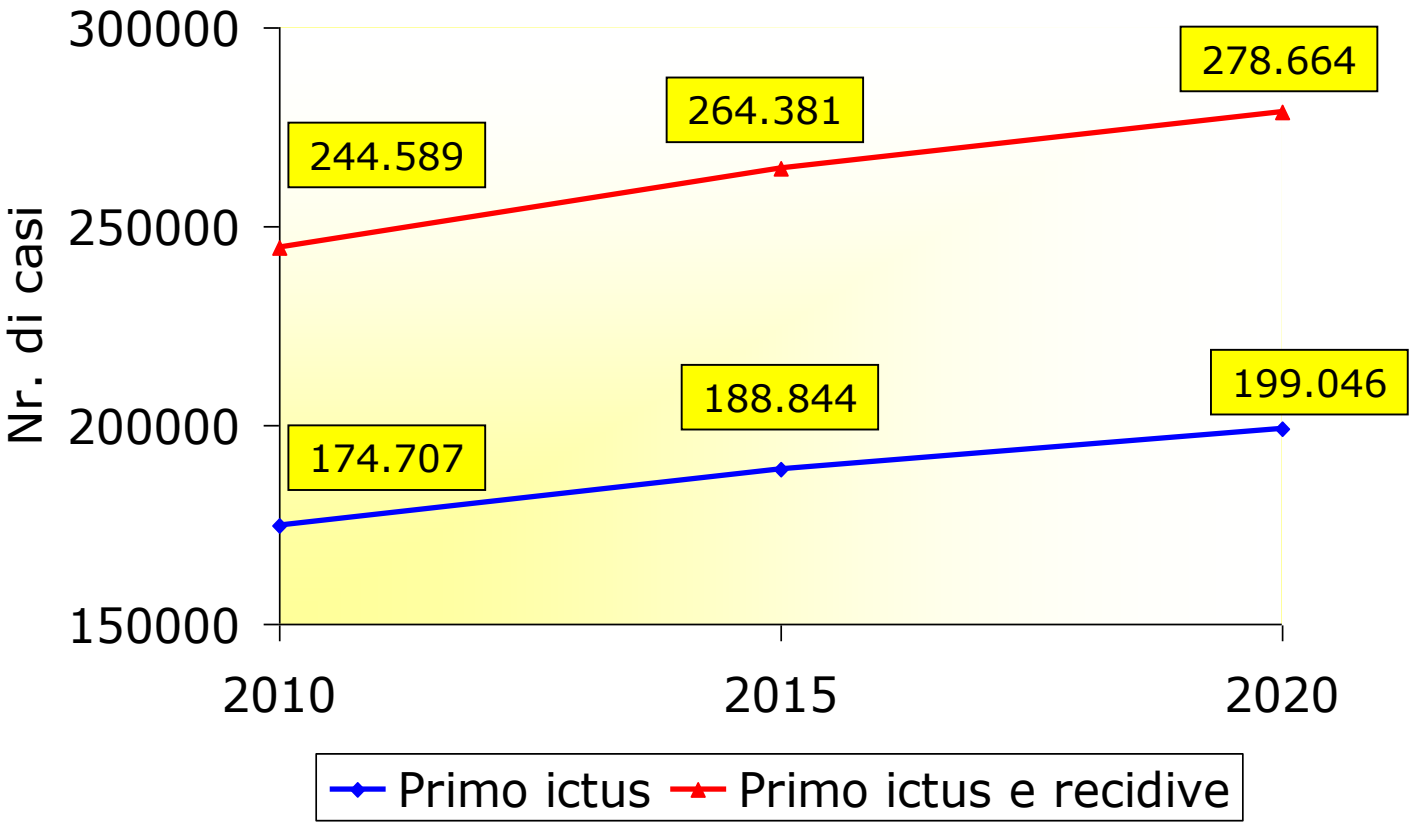
3,5 miliardi di euro spesi ogni anno per l’assistenza

Popolazione anziana in Italia: 1951-2041



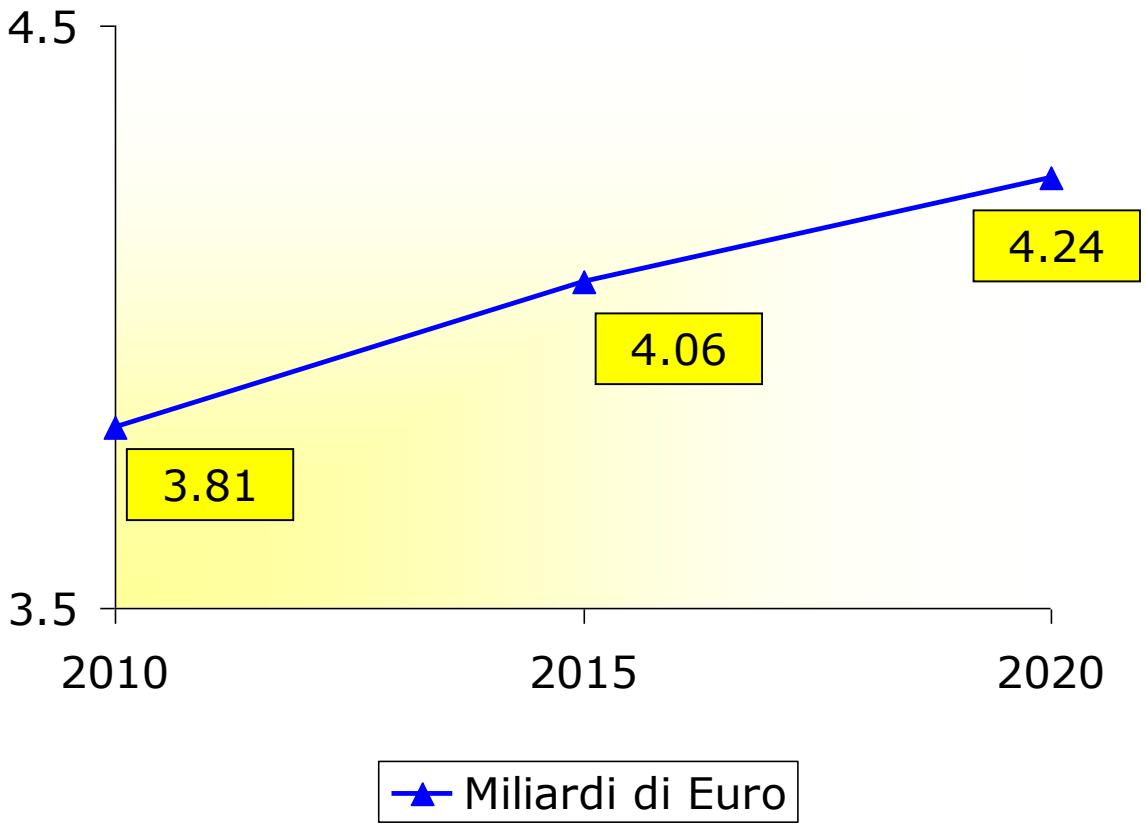
Fonte: IRP, ISTAT

Stime attuali e proiezioni al 2020 dei casi incidenti di ictus attesi nella popolazione italiana



Di Carlo AS, CNR, Ist. Neuroscienze, 2012

Stima dei costi diretti dell'ictus cerebrale sostenuti ogni anno dal Servizio Sanitario Nazionale e proiezioni al 2020.



Di Carlo AS, CNR, Ist. Neuroscienze, 2012

Continuità dell'assistenza al paziente con ictus cerebrale (necessità di un sistema integrato di cura)

Fase della prevenzione

- ✓ Informazione ed educazione
- ✓ Diagnosi dei fattori di rischio
- ✓ Aderenza ai trattamenti
- ✓ Appropriatezza
- ✓ Medico di Medicina Generale
- ✓ Medico specialista
- ✓ Conoscenza dei sintomi
- ✓ Attacco ischemico transitorio
- ✓ Percorso organizzato

Fase acuta

- ✓ Fattore tempo
- ✓ Servizio di emergenza
- ✓ DEA (Trombolisi)
- ✓ Stroke Team
- ✓ Stroke Unit
- ✓ Riabilitazione precoce
- ✓ Dimissione guidata

Fase post-acuta

- ✓ Riabilitazione intensiva
- ✓ Riabilitazione estensiva
- ✓ Care-giver riabilitativo
- ✓ AFA
- ✓ Medico di Medicina Generale
- ✓ Prevenzione secondaria
- ✓ Supporto psicologico
- ✓ Supporto sociale

ICTUS UN'EMERGENZA SANITARIA SOTTOVALUTATA IN ITALIA

Perché questa malattia è una cenerentola

Sebbene colpisca una persona ogni quattro minuti e incida in modo pesante sulla spesa per la salute, poche risorse sono investite per prevenirlo e curarlo. Eppure...

■ di GIANNA MILANO

Anche se l'ictus occupa il terzo posto per mortalità in Italia, dopo le malattie cardiovascolari e il cancro; anche se causa il maggior numero di invalidità permanenti; anche se negli ultimi dieci anni i casi sono aumentati e le proiezioni prevedono un loro incremento, fenomeno dovuto anche all'invecchiamento della popolazione, l'ictus, sia per risorse investite in progetti di prevenzione sia per finanziamenti sanitari in strutture specializzate, le «stroke unit», è rimasto un po' la cenerentola delle malattie del sistema circolatorio, di cui fa parte con l'infarto. Di ictus infatti si parla meno che di infarto, per il quale da tempo esistono negli ospedali le famose unità coronariche. «Del resto, fino a quattro o cinque anni fa non c'era neppure un'associazione che si occupasse di questa malattia» dice Giuseppe D'Alessandro, coordinatore nazionale di Alice, l'Associazione per la lotta all'ictus cerebrale nata su scala nazionale nel 2000, che sta organizzando diverse sedi sul territorio.

L'ictus, che come un lampo sconvolge la galassia delle cellule cerebrali interrompendo i circuiti neuronali, è considerato un evento tanto inevitabile quanto incurabile. «Eppure, non è così. Se si interviene tempestivamente in unità specializzate, lo si può contrastare quando si è verificato ed evitare con opportuni programmi di prevenzione» afferma Livia Candelise, professore di neurologia all'università degli studi di Milano, che da anni si batte perché le «stroke unit» (stroke in inglese significa ictus) diventino una priorità nel piano sanitario nazionale. «Consentirebbero di organizzare i ricoveri; di eseguire gli esami per una tempestiva diagnosi, verificando con una tac o con una risonanza magnetica il tipo di ictus, ischemico o emorragico; e di intervenire in pazienti selezionati con i farmaci opportuni» spiega Vito Lepore, neurologo all'università di Bari e ricercatore al NegriSud.

Il trattamento d'emergenza è spesso fondamentale per sopravvivere a un ictus. Le primissime fasi sono le più critiche. «La finestra terapeutica dopo i primi sintomi è brevissima (tre ore) e sono minuti essenziali per limitare i danni» continua Lepore. Negli Usa, appurato che l'ictus non è emorragico, viene ▶

QUANDO IL DANNO È EVIDENTE

La risonanza magnetica visualizza il cervello di una donna di 72 anni colpita da un ictus emorragico.

- **DIFFICOLTÀ DELLA PAROLA**, di comprensione e senso di confusione.
- **OFFUSCAMENTO** improvviso o diminuzione della vista a un occhio o a entrambi.
- **GIRAMENTI DI TESTA**, perdita di equilibrio, mancanza di coordinazione nei movimenti, difficoltà improvvisa a camminare, caduta inspiegabile.
- **FORTE MAL DI TESTA** e vomito senza cause spiegabili.
- **DIFFICOLTÀ A DEGLUTIRE**.

Pericolo in agguato

In Italia l'ictus è la **terza causa di morte** dopo le malattie cardiovascolari e il cancro. E del **25%** di disabilità cronica.

- Ogni anno i nuovi casi sono **130** mila. E con il progressivo invecchiamento della popolazione sono destinati ad aumentare: nel 2016 saranno **180 mila**.
- L'**85%** degli ictus è causato dall'interruzione del flusso sanguigno verso il cervello da un trombo che ostruisce un vaso o da un embolo che chiude un'arteria: ictus ischemico o infarto cerebrale.
- Circa il **15%** degli ictus è dovuto alla rottura di un'arteria cerebrale, come in presenza di un'aneurisma (malformazione della parete arteriosa) o di un'emorragia: ictus emorragico.
- Il **75%** degli ictus colpisce persone con oltre **65 anni**.
- Su **100** persone colpite da ictus **20** muoiono entro il primo mese; **30** restano invalide in modo permanente; **40** riprendono un'attività normale; e **10** recuperano completamente.
- Studi dimostrano che il ricovero in unità specializzate per l'ictus, analogie a quelle coronariche per l'infarto, aumenta del **20-30%** il numero dei sopravvissuti in condizioni di autonomia.
- In fase sperimentale in Italia è l'utilizzo entro tre ore dall'attacco ischemico di farmaci trombolitici, solo se l'ictus è ischemico e non emorragico.
- Il costo sanitario globale per un paziente di ictus è di **50 mila** euro. La patologia incide sulla spesa annuale sanitaria per circa **7 miliardi** di euro: il **10%** per le cure in fase acuta e il **90%** per assistenza e ricoveri successivi.

Ictus ischemico acuto: argomenti

- Evidenza di efficacia/sicurezza di trombolisi ev o trattamento endovascolare
- Effetto di tempo di trattamento
- Possibili determinanti con elevato impatto nell'anziano: ictus associato a fibrillazione atriale, disabilità pre-morbosa
- Effetto della leukoaraiosi

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

Jonathan Emberson, Kennedy R Lees*, Patrick Lyden*, Lisa Blackwell, Gregory Albers, Erich Bluhmki, Thomas Brott, Geoff Cohen, Stephen Davis, Geoffrey Donnan, James Grotta, George Howard, Markku Kaste, Masatoshi Koga, Ruediger von Kummer, Maarten Lansberg, Richard I Lindley, Gordon Murray, Jean Marc Olivot, Mark Parsons, Barbara Tilley, Danilo Toni, Kazunori Toyoda, Nils Wahlgren, Joanna Wardlaw, William Whiteley, Gregory J del Zoppo, Colin Baigent†, Peter Sandercock†, Werner Hacke†; for the Stroke Thrombolysis Trialists' Collaborative Group*

Emberson J, et al. The Lancet 2014

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

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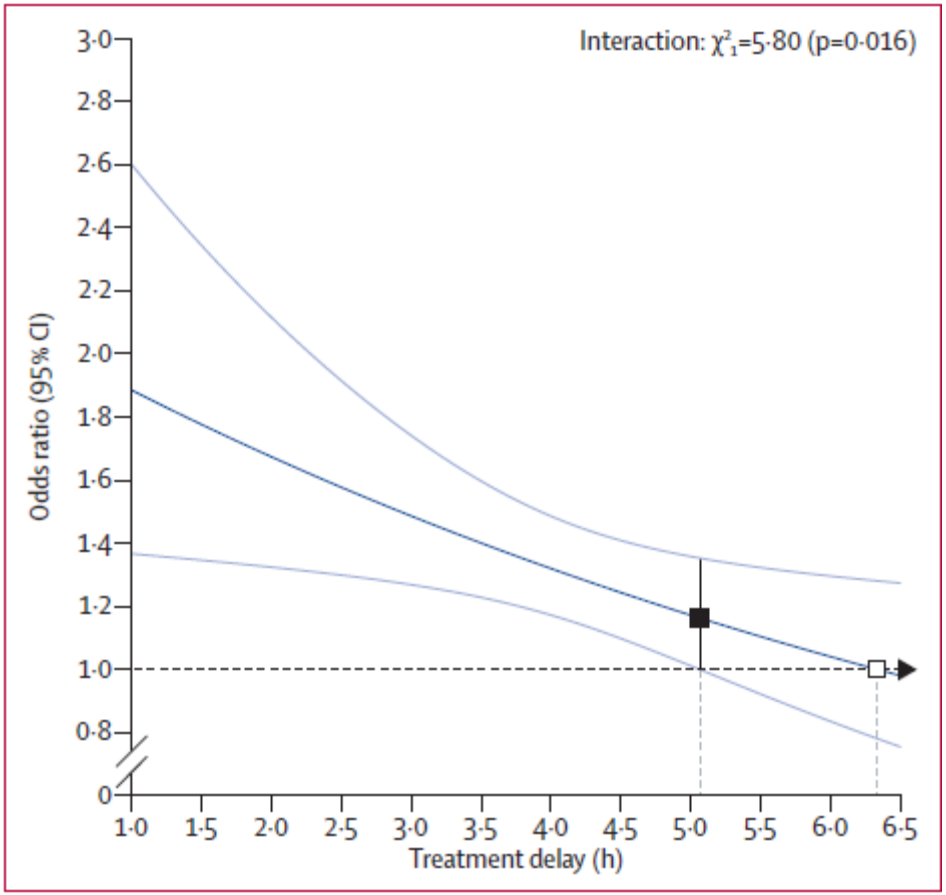


Figure 1: **Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)**

Emberson J, et al. The Lancet 2014

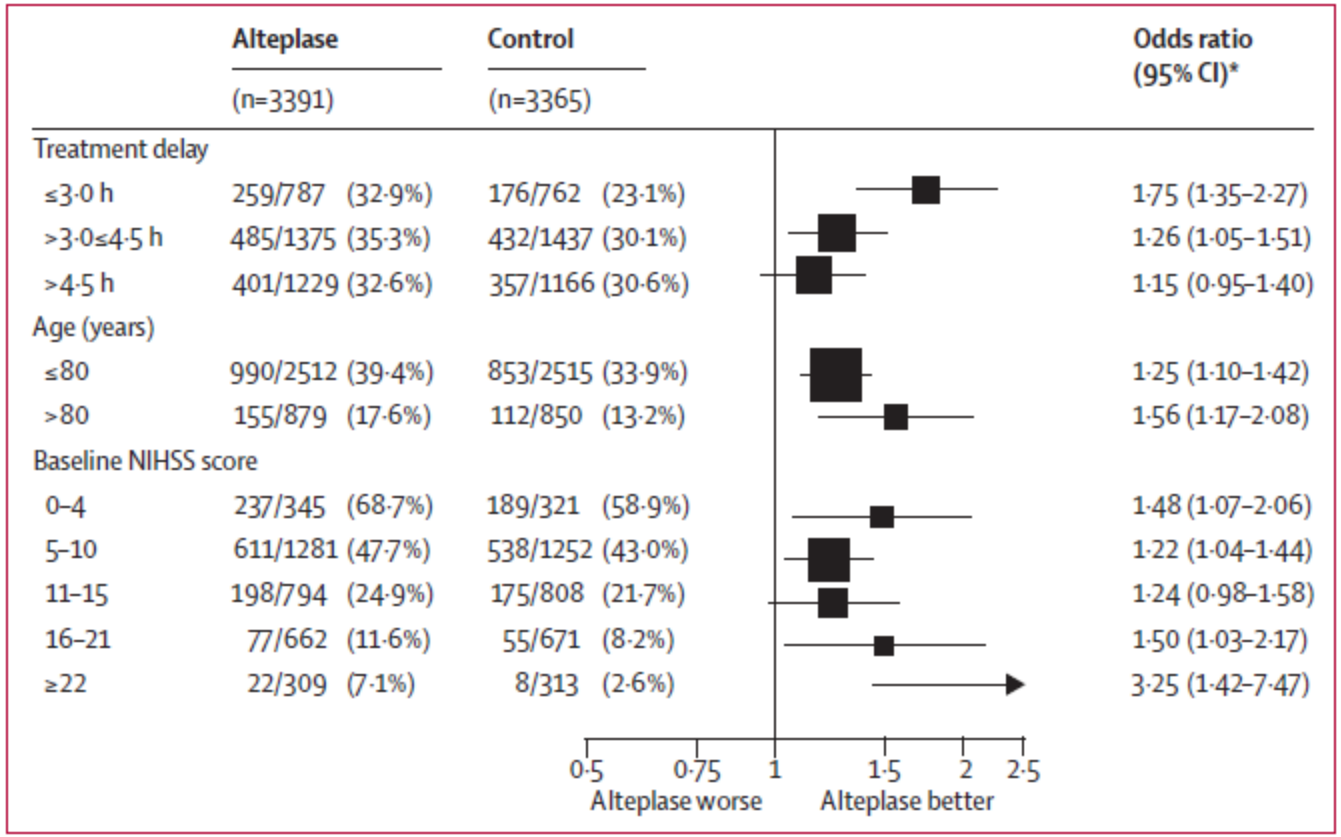


Figure 2: **Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity**
*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.

Emberson J, et al. The Lancet 2014

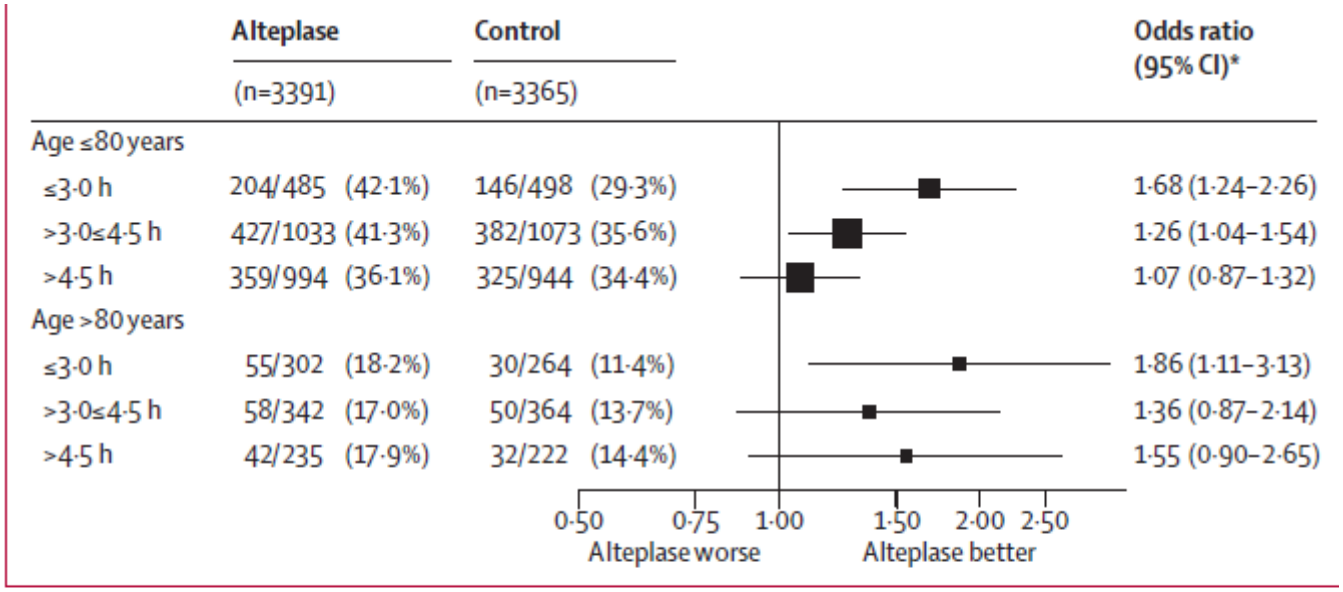


Figure 3: **Effect of alteplase on a good stroke outcome (mRS 0–1) by age, with different treatment delays**
Effect of age on the interaction between treatment delay and treatment effect p=0·08 (ie, not significant but, if anything, in the direction of it lengthening, not shortening, the period during which alteplase is effective in older people). *All six estimates derived from a single stratified logistic regression model that enables the odds ratio to be estimated separately for each group (also adjusted for baseline National Institutes of Health Stroke Scale score). mRS=modified Rankin Scale.

Emberson J, et al. The Lancet 2014

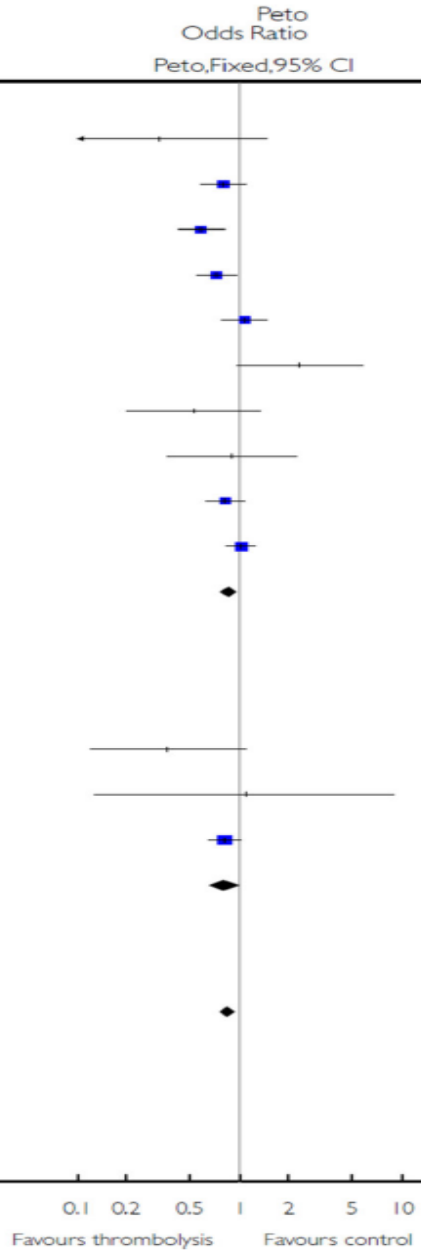
Review: Thrombolysis for acute ischaemic stroke

Comparison: 1 Any thrombolytic agent versus control

Cochrane review 2013

Outcome: 31 Death or dependency (mRS 3 to 6) by the end of follow-up; participants treated up to 6 hours aged ≤ 80 years versus > 80 years

Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Participants aged ≤ 80 years					
Mori 1992	11/19	10/12		0.4 %	0.32 [0.07, 1.48]
ECASS 1995	171/313	185/307		9.7 %	0.79 [0.58, 1.09]
NINDS 1995	127/273	170/283		8.8 %	0.58 [0.42, 0.81]
ECASS II 1998	187/409	211/391		12.8 %	0.72 [0.55, 0.95]
ATLANTIS B 1999	141/307	135/306		9.7 %	1.08 [0.78, 1.48]
ATLANTIS A 2000	64/71	56/71		1.2 %	2.35 [0.95, 5.82]
Wang 2003	14/67	11/33		1.1 %	0.52 [0.20, 1.35]
EPITHET 2008	18/38	18/36		1.2 %	0.90 [0.36, 2.23]
ECASS 3 2008	140/418	155/403		12.1 %	0.81 [0.61, 1.07]
IST3 2012	367/698	374/720		22.6 %	1.03 [0.83, 1.26]
Subtotal (95% CI)	**2613**	**2562**		**79.4 %**	**0.85 [0.76, 0.95]**
Total events: 1240 (Thrombolysis), 1325 (Control)					
Heterogeneity: $Chi^2 = 19.38$, df = 9 (P = 0.02); $I^2 = 54\%$					
Test for overall effect: Z = 2.85 (P = 0.0044)					
2 Participants aged > 80 years					
NINDS 1995	13/25	22/29		0.8 %	0.36 [0.12, 1.09]
EPITHET 2008	11/13	10/12		0.2 %	1.10 [0.13, 8.92]
IST3 2012	594/817	612/800		19.5 %	0.82 [0.65, 1.02]
Subtotal (95% CI)	**855**	**841**		**20.6 %**	**0.80 [0.64, 0.99]**
Total events: 618 (Thrombolysis), 644 (Control)					
Heterogeneity: $Chi^2 = 2.14$, df = 2 (P = 0.34); $I^2 = 7\%$					
Test for overall effect: Z = 2.06 (P = 0.040)					
Total (95% CI)	**3468**	**3403**		**100.0 %**	**0.84 [0.76, 0.93]**
Total events: 1858 (Thrombolysis), 1969 (Control)					
Heterogeneity: $Chi^2 = 21.82$, df = 12 (P = 0.04); $I^2 = 45\%$					
Test for overall effect: Z = 3.47 (P = 0.00052)					
Test for subgroup differences: $Chi^2 = 0.29$, df = 1 (P = 0.59), $I^2 = 0.0\%$					



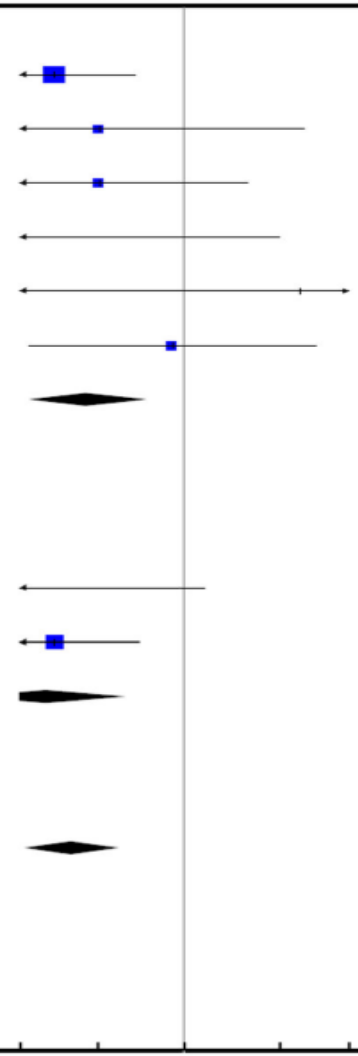
Review: Thrombolysis for acute ischaemic stroke

Comparison: 1 Any thrombolytic agent versus control

Cochrane review 2013

Outcome: 32 Death or dependency (mRS 3 to 6) by the end of follow-up, participants treated within 3 hours aged ≤ 80 years versus > 80 years

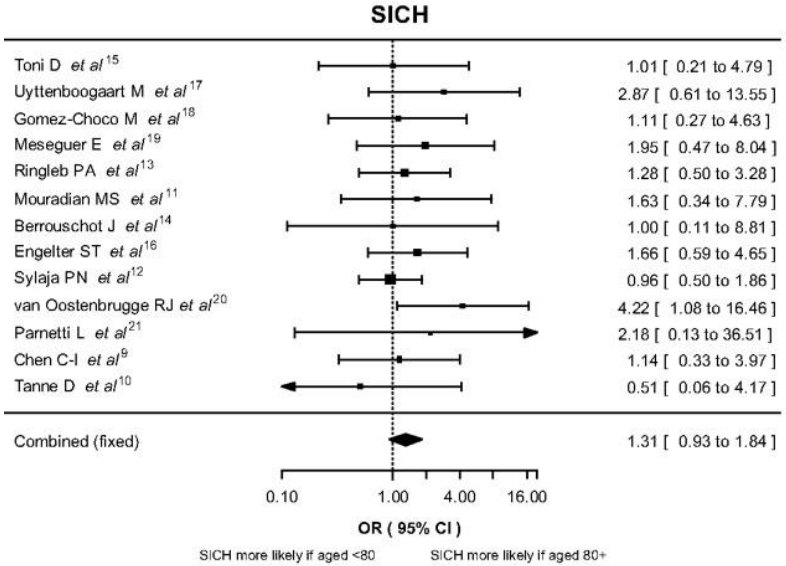
Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Participants aged ≤ 80 years					
NINDS 1995	127/273	170/283		35.6 %	0.58 [0.42, 0.81]
ECASS 1995	28/49	25/38		5.3 %	0.70 [0.29, 1.66]
ECASS II 1998	39/81	44/77		10.2 %	0.70 [0.37, 1.30]
ATLANTIS B 1999	3/13	12/26		2.2 %	0.39 [0.10, 1.49]
ATLANTIS A 2000	7/10	7/12		1.4 %	1.62 [0.29, 8.90]
IST3 2012	54/87	57/90		10.7 %	0.95 [0.52, 1.74]
Subtotal (95% CI)	**513**	**526**		**65.3 %**	**0.66 [0.52, 0.85]**
Total events: 258 (Thrombolysis), 315 (Control)					
Heterogeneity: Chi² = 3.64, df = 5 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 3.28 (P = 0.0010)					
2 Participants aged > 80 years					
NINDS 1995	13/25	22/29		3.2 %	0.36 [0.12, 1.09]
IST3 2012	245/344	266/328		31.5 %	0.58 [0.41, 0.83]
Subtotal (95% CI)	**369**	**357**		**34.7 %**	**0.56 [0.40, 0.78]**
Total events: 258 (Thrombolysis), 288 (Control)					
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² =0.0%					
Test for overall effect: Z = 3.41 (P = 0.00066)					
Total (95% CI)	**882**	**883**		**100.0 %**	**0.62 [0.51, 0.76]**
Total events: 516 (Thrombolysis), 603 (Control)					
Heterogeneity: Chi² = 4.98, df = 7 (P = 0.66); I² =0.0%					
Test for overall effect: Z = 4.66 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² =0.0%					

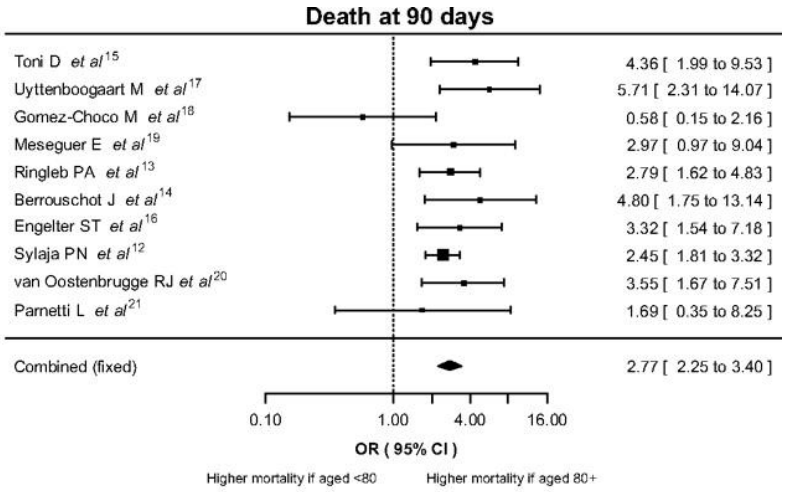


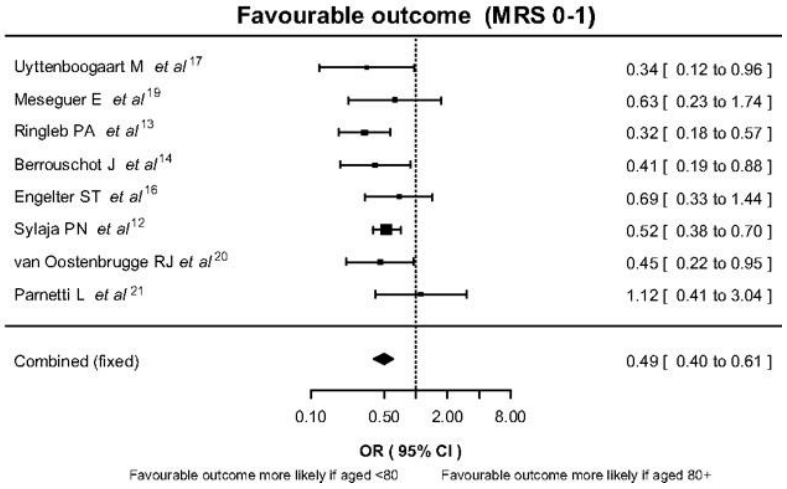
0.5 0.7 1 1.5 2

Favours thrombolysis Favours control

Forest plots showing effect of age group on symptomatic intracranial haemorrhage (SICH), risk of death at 3 months/90 days and probability of favourable outcome on the modified Rankin scale (mRS)—OR (fixed effects) meta-analysis plots.







Pallav Bhatnagar et al. J Neurol Neurosurg Psychiatry 2011;82:712-717

Intravenous thrombolysis for acute ischaemic stroke in the elderly: data from the Baden-Wuerttemberg stroke registry

B. Reuter[a,b], C. Gumbinger[c], T. Sauer[a], H. Wiethölter[d], I. Bruder[e], S. Rode[e], P. A. Ringleb[c], R. Kern[a], W. Hacke[c] and M. G. Hennerici[a] Stroke Working Group of Baden-Wuerttemberg*

Table 4 Outcome mRS ≤2 at discharge

Age group	Thrombolytic therapy *n* (%)	No thrombolytic therapy *n* (%)	Adjusted OR (95% CI)	*P* value
<50 years	667 (65)	3622 (82)	1.69 (1.31, 2.18)	<0.0001
50–59 years	1042 (61)	6202 (76)	1.94 (1.60, 2.36)	<0.0001
60–69 years	1835 (54)	11 867 (71)	1.73 (1.50, 2.00)	<0.0001
70–79 years	3499 (45)	23 213 (64)	1.87 (1.68, 2.08)	<0.0001
80–89 years	2849 (32)	22 509 (46)	1.90 (1.69, 2.14)	<0.0001
≥90 years	394 (17)	4014 (30)	1.61 (1.13, 2.31)	0.009
Overall	10 286 (45)	71 427 (60)	1.84 (1.73, 1.96)	<0.0001

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.
Numbers do not add up to group totals in Table 1 due to missing values in the outcome variable.

European Journal of Neurology 2015, **0**: 1–8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

Joseph P. Broderick, M.D., Yuko Y. Palesch, Ph.D., Andrew M. Demchuk, M.D., Sharon D. Yeatts, Ph.D., Pooja Khatri, M.D., Michael D. Hill, M.D., Edward C. Jauch, M.D., Tudor G. Jovin, M.D., Bernard Yan, M.D., Frank L. Silver, M.D., Rüdiger von Kummer, M.D., Carlos A. Molina, M.D., Bart M. Demaerschalk, M.D., Ronald Budzik, M.D., Wayne M. Clark, M.D., Osama O. Zaidat, M.D., Tim W. Malisch, M.D., Mayank Goyal, M.D., Wouter J. Schonewille, M.D., Mikael Mazighi, M.D., Ph.D., Stefan T. Engelter, M.D., Craig Anderson, M.D., Ph.D., Judith Spilker, R.N., B.S.N., Janice Carrozzella, R.N., B.A., R.T.(R.), Karla J. Ryckborst, R.N., B.N., L. Scott Janis, Ph.D., Renée H. Martin, Ph.D., Lydia D. Foster, M.S., and Thomas A. Tomsick, M.D., for the Interventional Management of Stroke (IMS) III Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H., Jeffry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D., Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D., Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D., Max Wintermark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

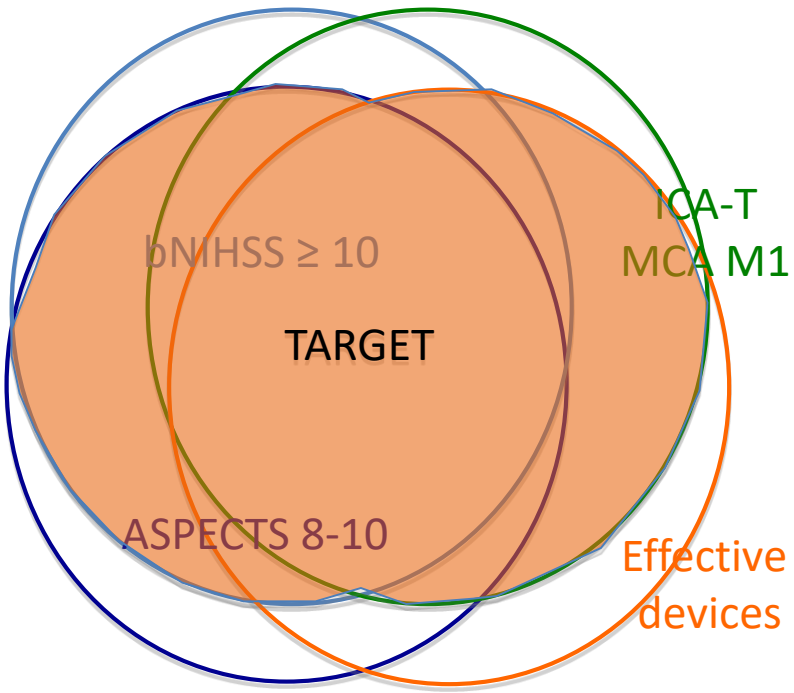
ORIGINAL ARTICLE

Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*

NEJM, March 2013

New clinical paradigms on EVT to enrich favorable response



Key Points For Future Trials

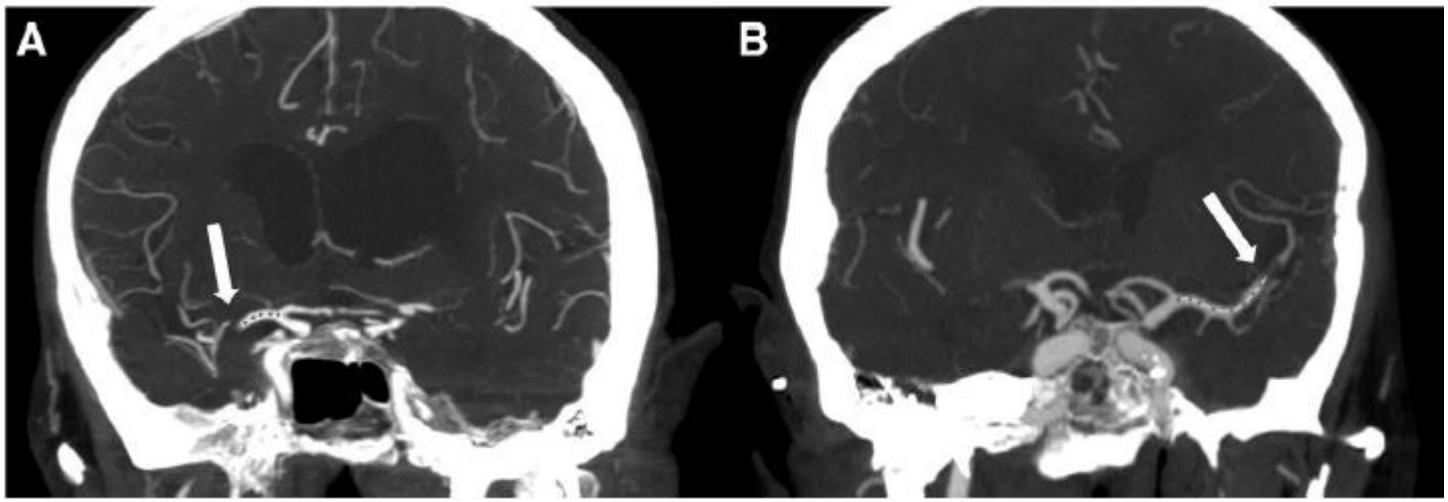
1. Major vascular occlusion

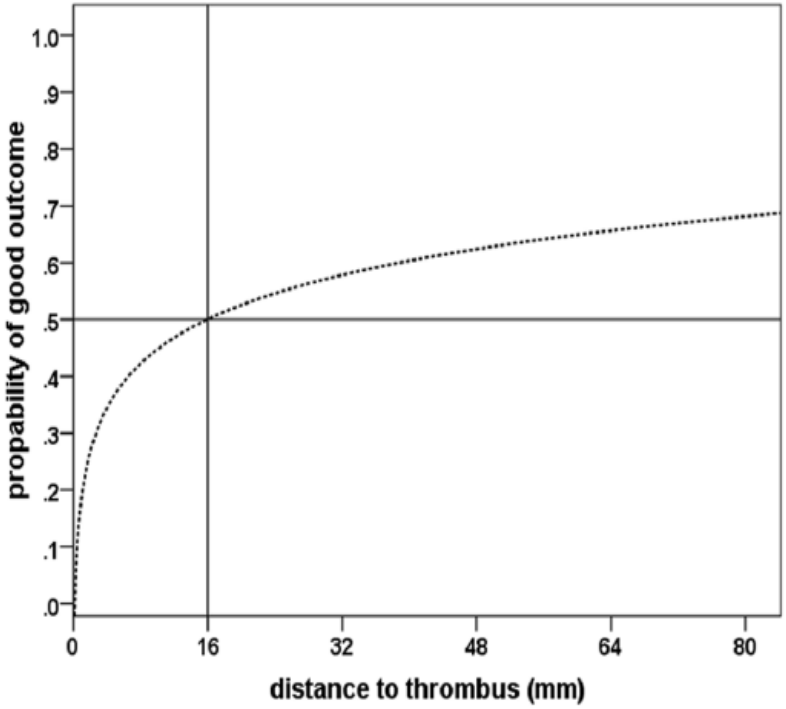
2. Salvageable brain (small core)

3. Fast & effective revascularization

4. tPA eligible and non-eligible patients

Nogueira R, Gupta R and Davalos A. Stroke 2013





Distance to thrombus and good outcome,

Friedrich B, Stroke 2015

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

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*

ORIGINAL ARTICLE

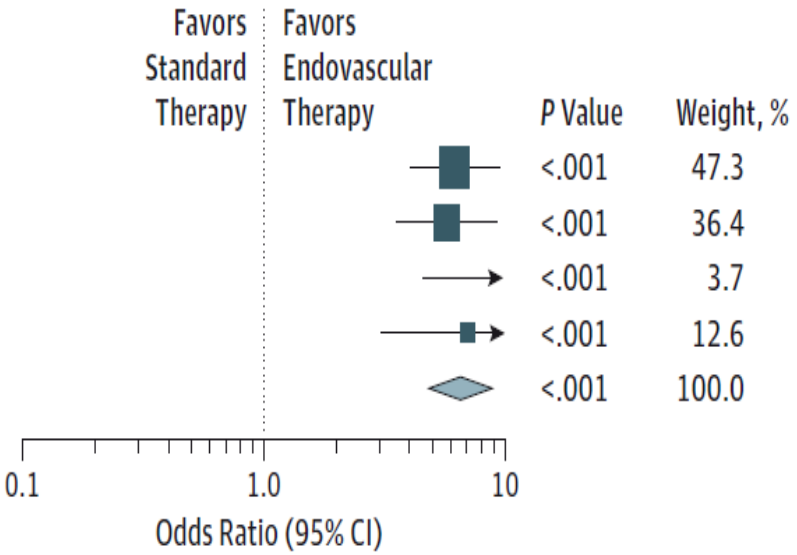
Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

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*

C Revascularization at 24 h

Source	Endovascular Therapy Events/No.	Standard Therapy Events/No.	Odds Ratio (95% CI)	*P* Value	Weight, %
MR CLEAN,[29] 2015	141/187	68/207	6.27 (4.03-9.74)	<.001	47.3
ESCAPE,[30] 2015	113/156	43/138	5.81 (3.51-9.60)	<.001	36.4
EXTEND-IA,[31] 2015	33/35	15/35	22.00 (4.55-106.43)	<.001	3.7
SWIFT-PRIME,[32] 2015	53/64	21/52	7.11 (3.03-16.70)	<.001	12.6
Overall	340/442	147/432	6.49 (4.79-8.79)	<.001	100.0

$I^2 = 0.0\%$, $P = .46$

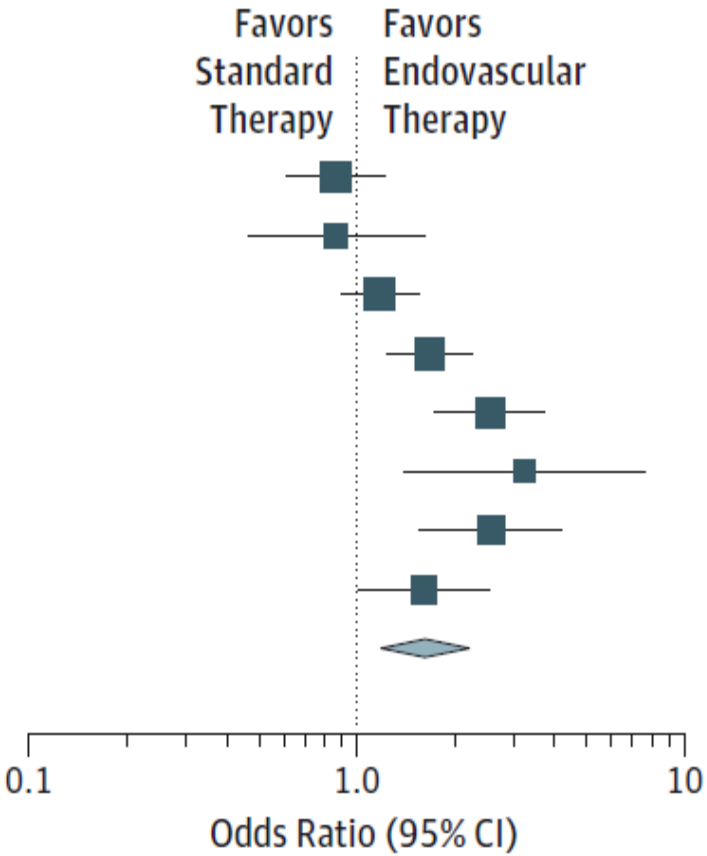


D Symptomatic intracranial hemorrhage within 90 d

B Reduced disability at 90 d

Source	Odds Ratio (95% CI)	*P* Value	Weight, %
SYNTHESIS,[26] 2013	0.86 (0.60-1.23)	.40	14.2
MR RESCUE,[27] 2013	0.86 (0.45-1.63)	.65	10.1
IMS III,[28] 2013	1.17 (0.88-1.57)	.28	15.3
MR CLEAN,[29] 2015	1.66 (1.22-2.28)	.001	14.9
ESCAPE,[30] 2015	2.53 (1.70-3.79)	<.001	13.6
EXTEND-IA,[31] 2015	3.22 (1.36-7.61)	.008	7.5
SWIFT-PRIME,[32] 2015	2.55 (1.53-4.26)	<.001	11.9
REVASCAT,[33] 2015	1.57 (0.97-2.55)	.07	12.4
Overall	1.56 (1.14-2.13)	.005	100.0

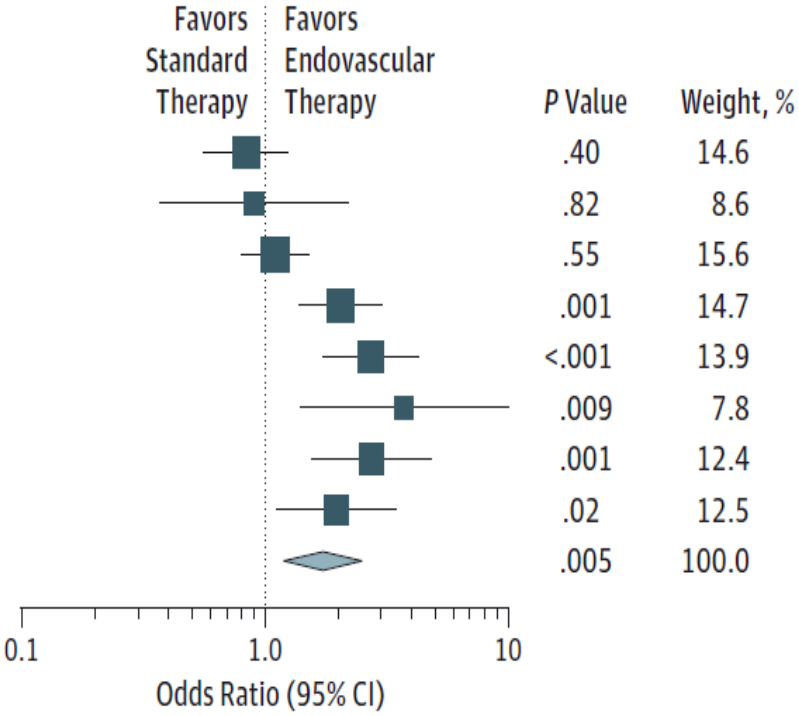
$I^2 = 75.9\%$, $P < .01$



A Functional independence (modified Rankin Scale score 0-2) at 90 d

Source	Endovascular Therapy Events/No.	Standard Therapy Events/No.	Odds Ratio (95% CI)	*P* Value	Weight, %
SYNTHESIS,[26] 2013	76/181	84/181	0.84 (0.55-1.27)	.40	14.6
MR RESCUE,[27] 2013	12/64	11/54	0.90 (0.36-2.25)	.82	8.6
IMS III,[28] 2013	177/415	86/214	1.11 (0.79-1.55)	.55	15.6
MR CLEAN,[29] 2015	76/233	51/267	2.05 (1.36-3.09)	.001	14.7
ESCAPE,[30] 2015	87/164	43/147	2.73 (1.71-4.37)	<.001	13.9
EXTEND-IA,[31] 2015	25/35	14/35	3.75 (1.38-10.17)	.009	7.8
SWIFT-PRIME,[32] 2015	59/98	33/93	2.75 (1.53-4.94)	.001	12.4
REVASCAT,[33] 2015	45/103	29/103	1.98 (1.11-3.53)	.02	12.5
Overall	557/1293	351/1094	1.71 (1.18-2.49)	.005	100.0

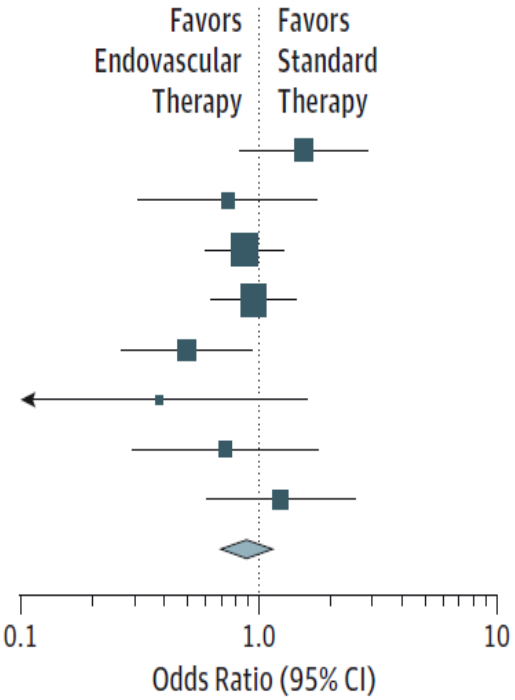
$I^2 = 75.4\%$, $P<.01$



B Mortality at 90 d

Source	Endovascular Therapy Events/No.	Standard Therapy Events/No.	Odds Ratio (95% CI)	*P* Value	Weight, %
SYNTHESIS,[26] 2013	26/181	18/181	1.52 (0.80-2.88)	.20	12.5
MR RESCUE,[27] 2013	12/64	13/54	0.73 (0.30-1.76)	.48	7.2
IMS III,[28] 2013	83/434	48/222	0.86 (0.58-1.28)	.45	25.3
MR CLEAN,[29] 2015	49/233	59/267	0.94 (0.61-1.44)	.77	23.1
ESCAPE,[30] 2015	17/164	28/147	0.49 (0.26-0.94)	.03	12.3
EXTEND-IA,[31] 2015	3/35	7/35	0.38 (0.09-1.59)	.18	2.9
SWIFT-PRIME,[32] 2015	9/98	12/97	0.72 (0.29-1.79)	.47	6.8
REVASCAT,[33] 2015	19/103	16/103	1.23 (0.59-2.55)	.58	10.1
Overall	218/1312	201/1106	0.87 (0.68-1.12)	.27	100.0

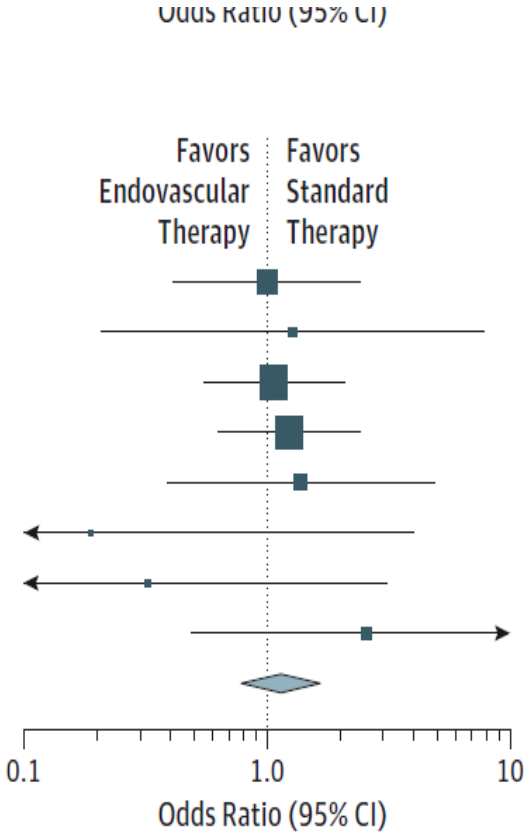
$I^2 = 17.7\%$, $P = .29$



D Symptomatic intracranial hemorrhage within 90 d

Source	Endovascular Therapy Events/No.	Standard Therapy Events/No.	Odds Ratio (95% CI)	*P* Value	Weight, %
SYNTHESIS,[26] 2013	10/181	10/181	1.00 (0.41-2.46)	>.99	17.4
MR RESCUE,[27] 2013	3/64	2/54	1.28 (0.21-7.95)	.79	4.2
IMS III,[28] 2013	27/434	13/222	1.07 (0.54-2.11)	.85	30.4
MR CLEAN,[29] 2015	18/233	17/267	1.23 (0.62-2.45)	.55	30.0
ESCAPE,[30] 2015	6/165	4/150	1.38 (0.38-4.98)	.63	8.6
EXTEND-IA,[31] 2015	0/35	2/35	0.19 (0.01-4.08)	.29	1.5
SWIFT-PRIME,[32] 2015	1/98	3/97	0.32 (0.03-3.16)	.33	2.7
REVASCAT,[33] 2015	5/103	2/103	2.58 (0.49-13.59)	.27	5.1
Overall	70/1313	53/1109	1.12 (0.77-1.63)	.56	100.0

$I^2 = 0.0\%$, $P = .82$



AHA/ASA Guideline

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

Recommendations

Endovascular Interventions

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**

Systems of Stroke Care

1. **Patients should be transported rapidly to the closest available certified primary stroke center**

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)

ISO – SPREAD 2015

Trattamenti endoarteriosi

Raccomandazione

Grado A

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

Raccomandazione

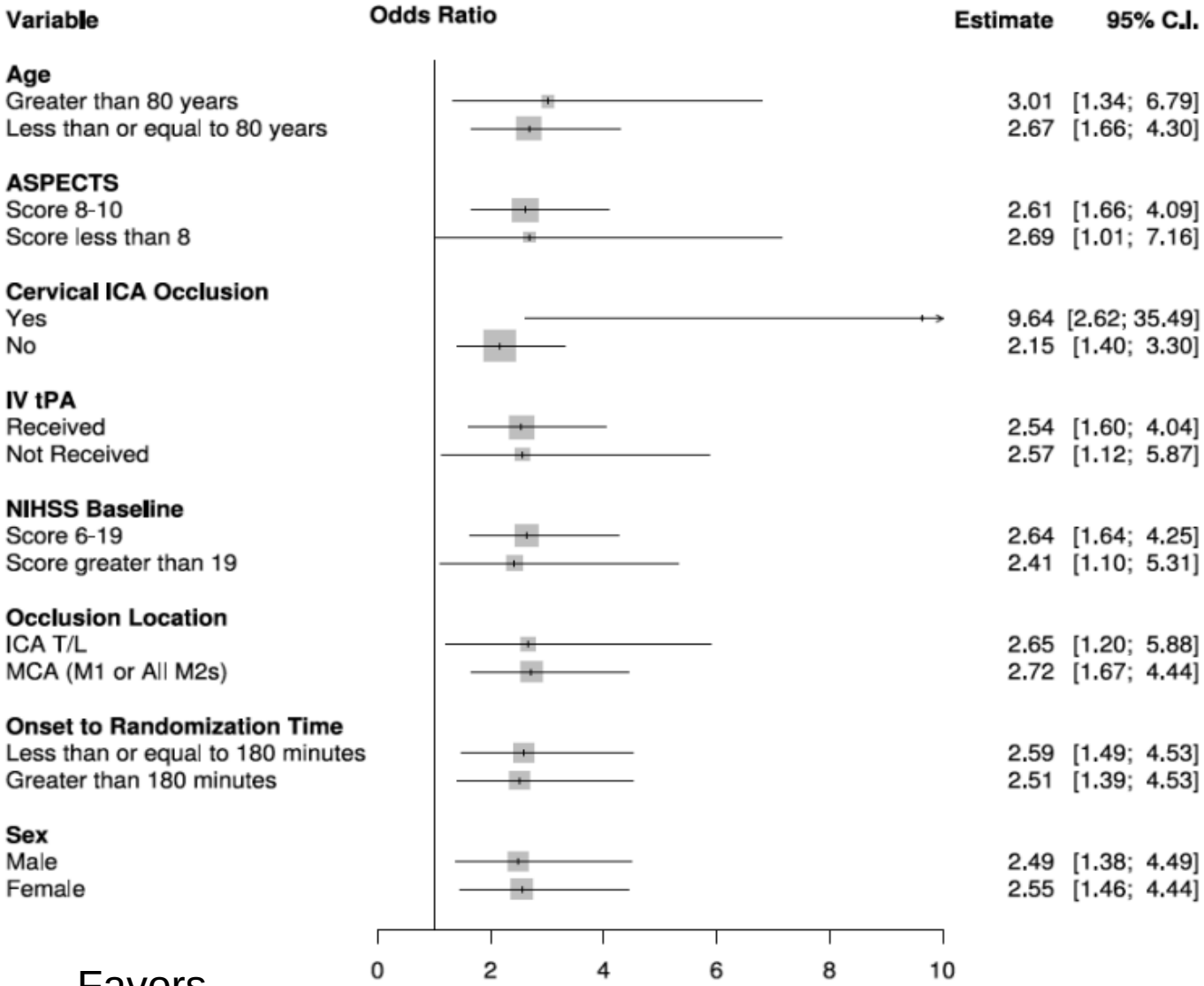
Grado B

Le tecniche di trombectomia meccanica sono indicate entro 6 ore dall'esordio dei sintomi in pazienti con occlusione di carotide interna intra-cranica, arteria cerebrale media tratti 1-2, arteria cerebrale anteriore tratto 1, che non rispondono o che non possono essere sottoposti alla trombolisi e.v.

Table 1. Representative stroke trials and the age of patients represented.

Clinical trials	Age of patients (years)
IMS-III	18–82
SYNTHESIS EXPANSION	18–80
SWIFT	22–85
PENUMBRA PIVOTAL TRIAL	63.5+/–13.5
MERCI	67+/–15.5
NINDS Part 1	<77
NINDS Part 2	<81
MR CLEAN	23–96 (IQR, 54.5–76)
ESCAPE	No upper age limit (IQR, 60–81)
EXTEND-IA	No upper age limit (oldest patient enrolled 81)

Subgroups



Favors Controls ⟵ ⟶ Favors intervention

Journal of Cerebrovascular and Endovascular Neurosurgery
pISSN 2234-8565, eISSN 2287-3139, *http://dx.doi.org/10.7461/jcen.2015.17.3.173*

Original Article

Endovascular Treatment for Acute Ischemic Stroke Patients over 80 Years of Age

Kihwan Hwang[1], Gyojun Hwang[1], O-Ki Kwon[1], Chang Hyeun Kim[1], Seung Pil Ban[1], Moon-Ku Han[2], Hee-Joon Bae[2], Beom Joon Kim[2], Jae Seung Bang[1], Chang Wan Oh[1], Boram Lee[1], Eun-A Jeong[1]

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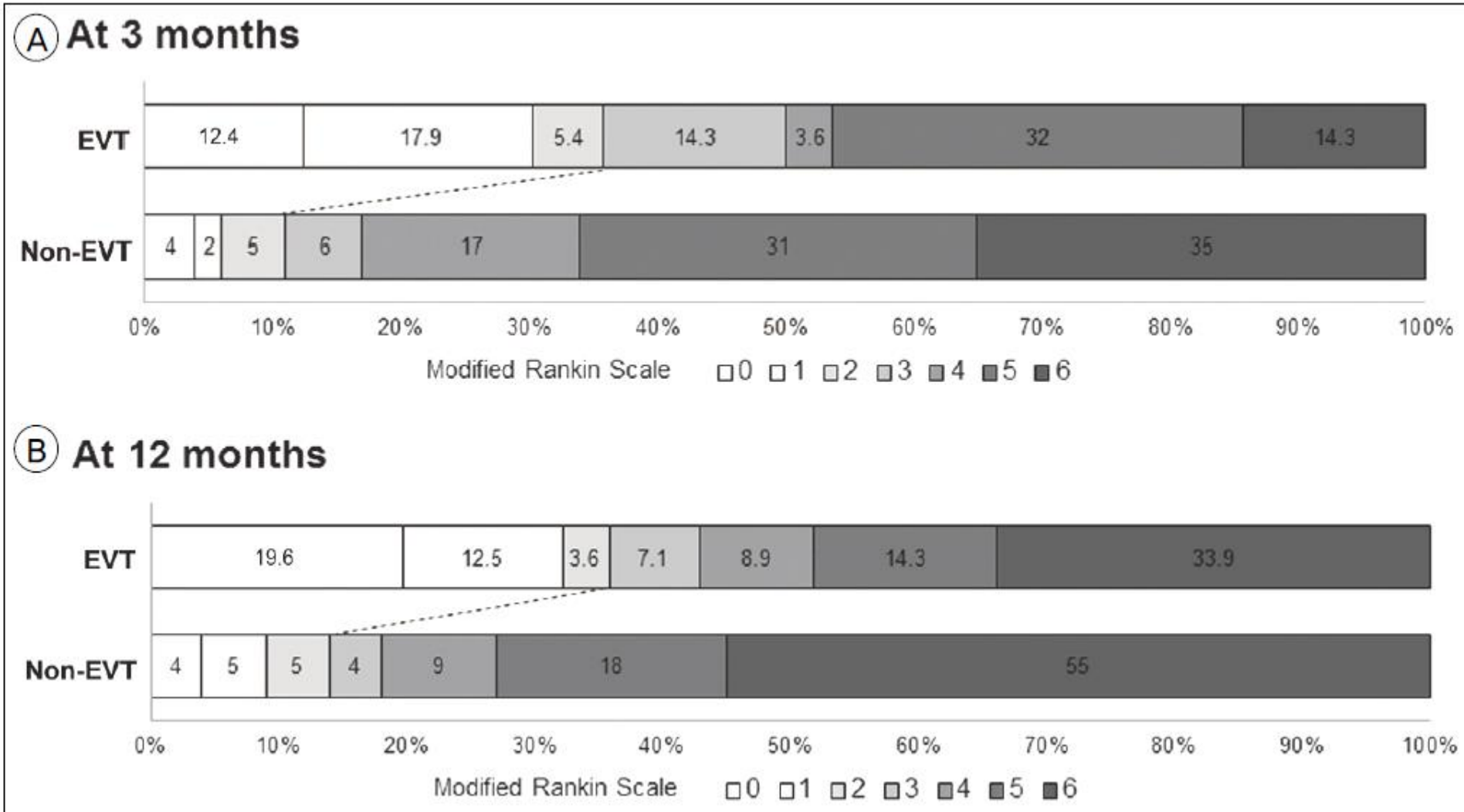

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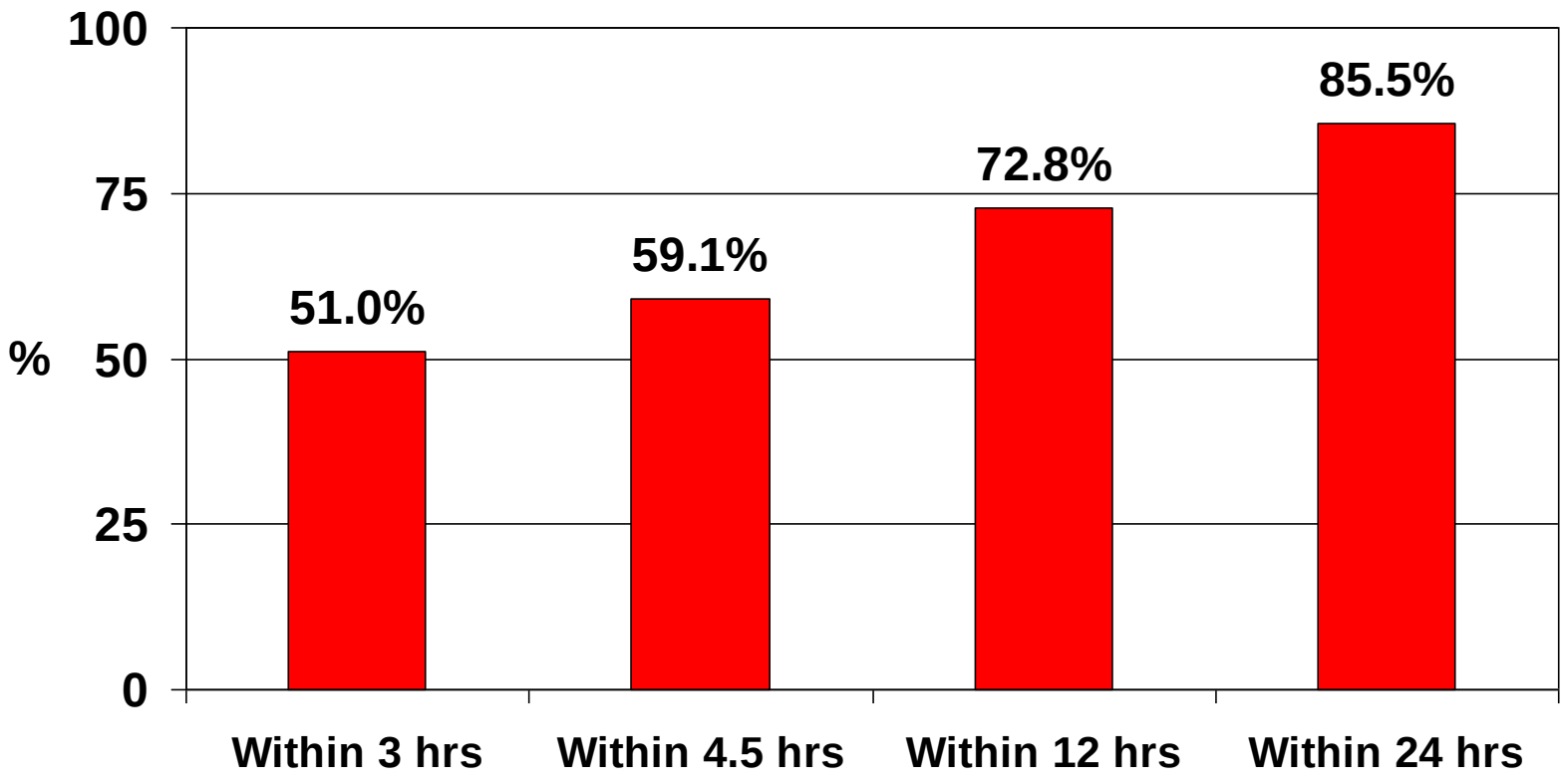
Table 2. Functional outcomes, in-hospital morbidities, symptomatic hemorrhages, and in-hospital mortalities in the EVT and non-EVT groups

	EVT (n = 56)	Non-EVT (n = 100)	Unadjusted odds ratio (95% confidence interval)	Adjusted† odds ratio (95% confidence interval)	*p* value
Good functional outcome (mRS 0-2)					
3 months	20 (35.7%)	11 (11.0%)	4.495 (1.957-10.322)	4.779 (1.972-11.579)	0.001
12 months	20 (35.7%)	14 (14.0%)	3.413 (1.555-7.490)	3.705 (1.574-8.722)	0.003
In-hospital morbidities					
Endotracheal intubation	10 (17.9%)	17 (17.0%)	1.061 (0.449-2.509)	1.062 (0.415-2.714)	0.901
Gastrointestinal bleeding	1 (1.8%)	8 (8.0%)	0.209 (0.025-1.717)	0.185 (0.022-1.585)	0.124
Pneumonia	7 (12.5%)	29 (29.0%)	0.350 (0.142-0.862)	0.262 (0.098-0.703)	0.008
Urinary tract infection	9 (16.1%)	34 (34.0%)	0.372 (0.163-0.848)	0.256 (0.099-0.657)	0.005
Symptomatic hemorrhage*	6 (10.7%)	2 (2.0%)	5.880 (1.145-30.196)	6.859 (1.139-41.317)	0.036
In-hospital mortality	7 (12.5%)	8 (8.0%)	1.643 (0.562-4.799)	1.380 (0.408-4.664)	0.604

EROS Study. Percentages of patients arriving to ER in the first 24 hours from stroke onset. Florence area



Regione Toscana

Servizio Sanitario della Toscana

A.L.I.Ce. Onlus Associazione per la Lotta all'Ictus Cerebrale

ICTUS

POCHI MINUTI VALGONO UNA VITA

RICONOSCI SUBITO I SINTOMI E CHIAMA IMMEDIATAMENTE IL 118

BOCCA STORTA
Chiedere di sorridere: la bocca tira da un lato, è asimmetrica.

BRACCIO DEBOLE
Chiedere di alzare entrambe le braccia in avanti: una delle braccia cade giù.

DIFFICOLTÀ A PARLARE
Controllare se la persona non riesce a parlare e/o non capisce. Chiedere di ripetere una semplice frase ("Il cielo è blu"). Non riesce a farlo bene. Parla farfugliando.

DIFFICOLTÀ NELLA VISTA
Verificare se la persona vede annebbiato, non vede metà degli oggetti, oppure vede doppio.

Oppure all'improvviso compare un forte **mal di testa mai provato prima**, accompagnato spesso da nausea, vomito, perdita di coscienza.

Campagna informativa regionale in collaborazione con Alice Toscana Onlus - Associazione per la lotta all'ictus cerebrale.

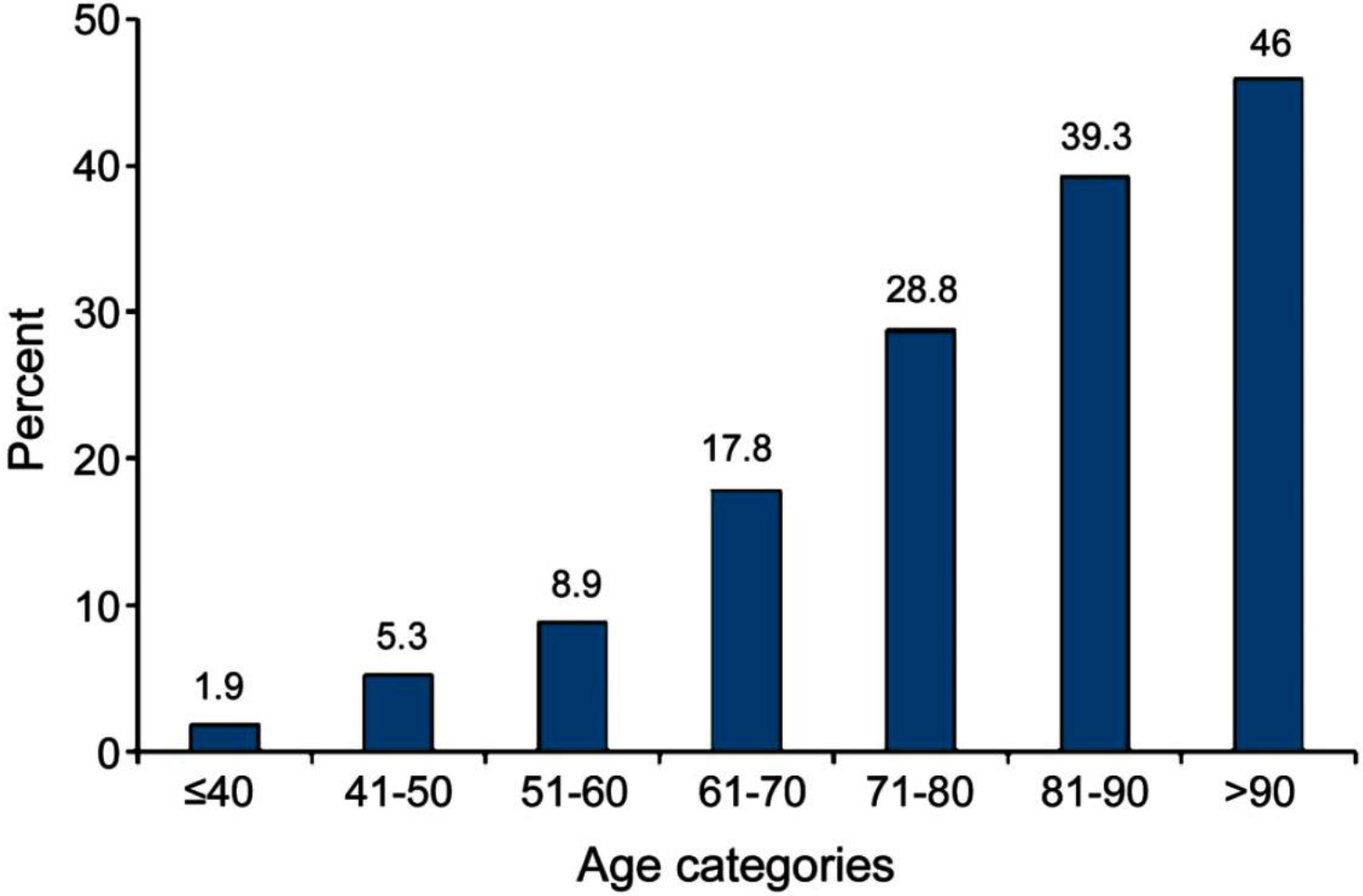
www.regione.toscana.it/ictus

METROPOLITANA DI FIRENZE GESTIONE DEL PERCORSO DIAGNOSTICO TERAPEUTICO ASSISTENZIALE NEI PAZIENTI CON ICTUS ISCHEMICO

Per i pazienti per i quali il cosiddetto "tempo ultimo visto sano" è inferiore o uguale a 6 ore e per quelli per i quali il "tempo ultimo visto sano" non è definibile, la Centrale Operativa 118 produce un ***"Codice Ictus"*** visibile sulla scheda da postazione informatica del PS DEA. L'inquadramento del paziente nel "*Codice Ictus"* comporta la produzione da parte della Centrale 118 di un alert telefonico che raggiunge il medico della stroke unit (349-2228937)ed il Punto di Presa in Carico PS DEA (055-7949354); Il medico della stroke unit provvede ad allertare il neuroradiologo (348-6527779) ed il neuroradiologo interventista (348-6527779).

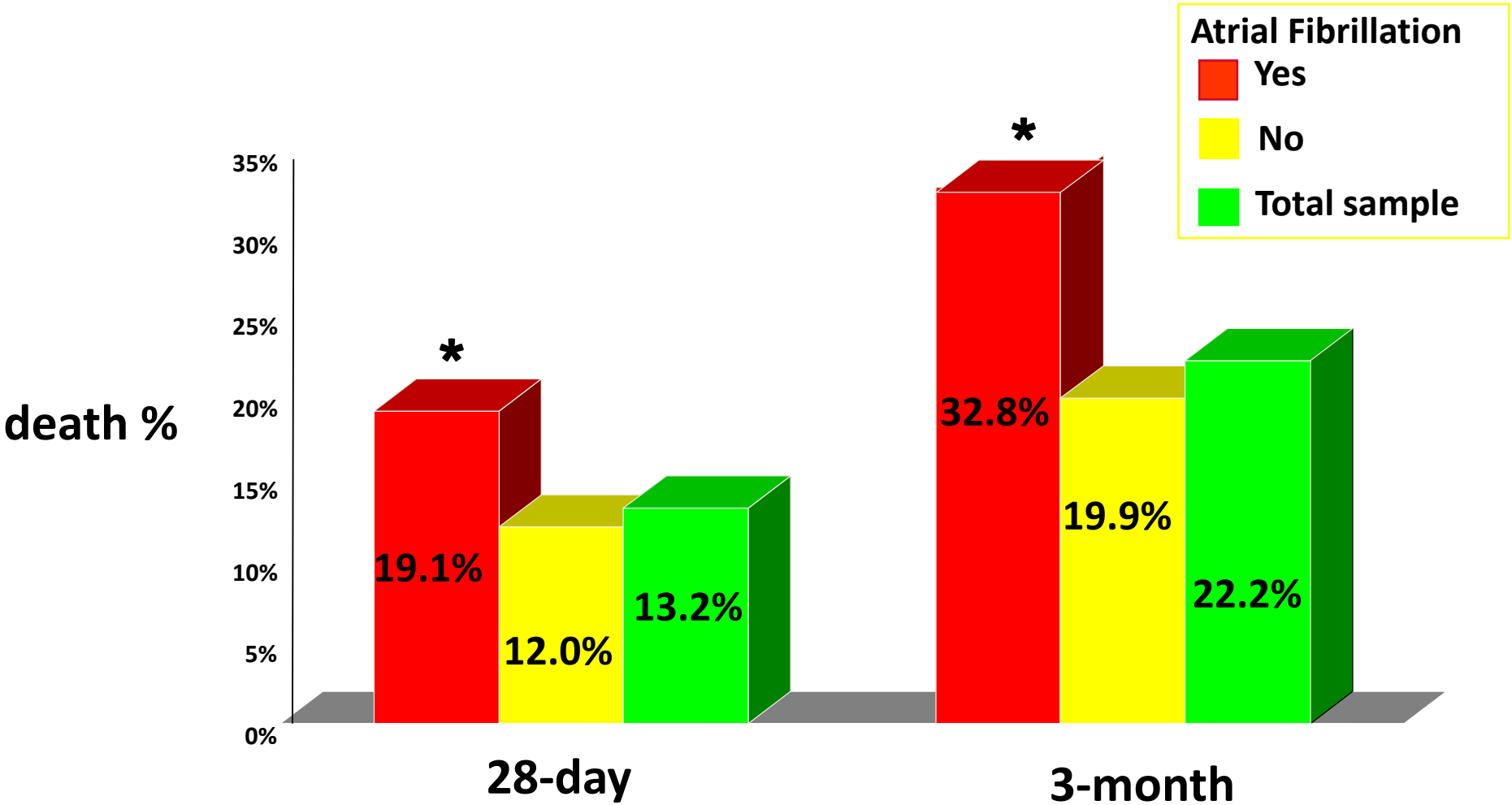
Stroke associato a fibrillazione atriale

Prevalence of Atrial Fibrillation in ischemic stroke patients by age group. The Canadian Stroke Network (n= 10 528)



Source: McGrath et al., Neurology, 2013

28-DAY AND 3-MONTH DEATHS



* p< 0.001

Lamassa M. et al, Stroke 2001

REGISTRO ENDOVASCOLARE ITALIANO - REI

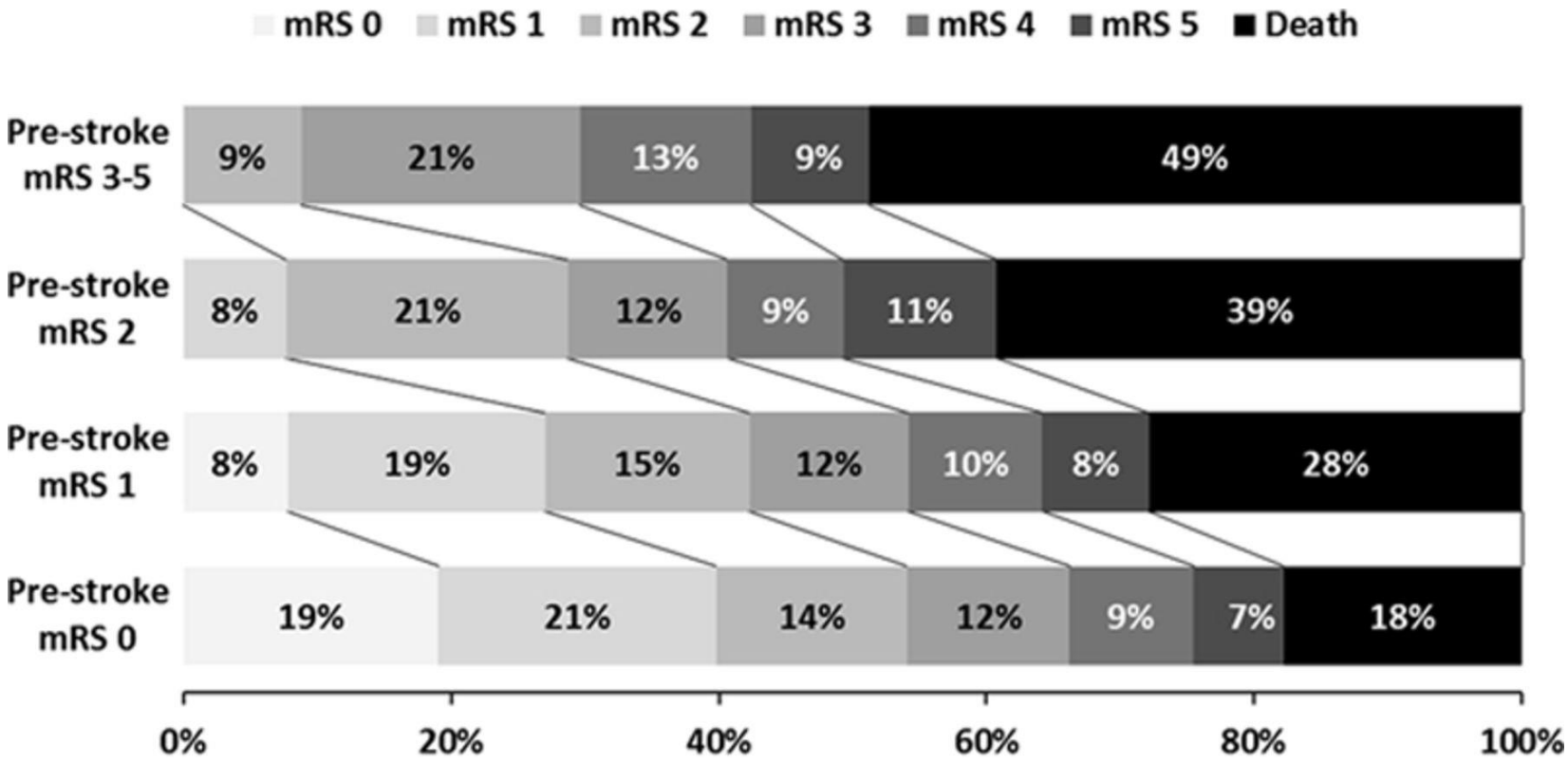
Fibrillazione atriale, outcome radiologico e clinico in 185 p. con età > 80 anni trattati negli anni 2011-2014.
Totale p. considerati: 1406
p. con età < 80: 1221 di cui 314 (26%) con FA
P. con età > 80: 185 (13% di 1406) di cui 92 (50%) con FA

	Fibrillazione atriale		
	Sì (N=92)	No (N=93)	P
Rivascolarizzazione efficace (TICI 2b-3)	61 (66%)	59 (63%)	0.683
Emorragia sintomatica 24 h	9 (10%)	5 (6%)	0.275
Indipendenza funzionale 3 mesi (mRankin 0-2)	21 (23%)	23 (25%)	0.761
Morti a tre mesi	27 (29%)	22 (24%)	0.380

Mangiafico S, et al., unpublished data

Trombolisi e disabilità pre-stroke

Distribution of modified Rankin Scale (mRS) scores 3 months after the onset of stroke according to preexisting disability.



Michal Karlinski et al. Stroke. 2014;45:770-775

Effects of thrombolysis for acute stroke in patients with pre-existing disability

R. Blaine Taylor Foell, Brian Silver, Jose G. Merino, Edward H. Wong, Bart M. Demaerschalk, Fali Poncha, Arturo Tamayo, Vladimir Hachinski

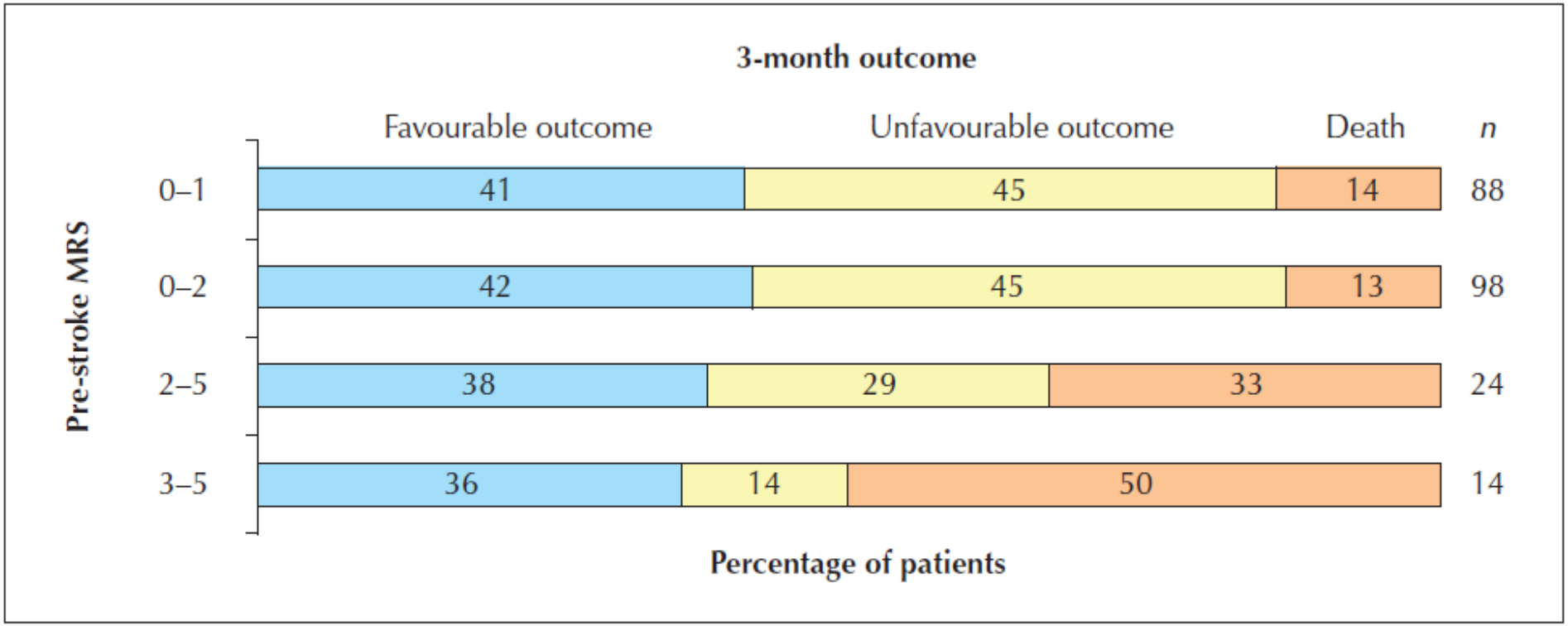


Fig. 2: Unadjusted proportions of the same patients by 3-month favourable or unfavourable outcome, a favourable outcome being defined as either an MRS score of 0 or 1, or, for patients with an MRS score greater than 1 before the stroke, a return to the prestroke MRS score.

Effetto della leukoaraiosi

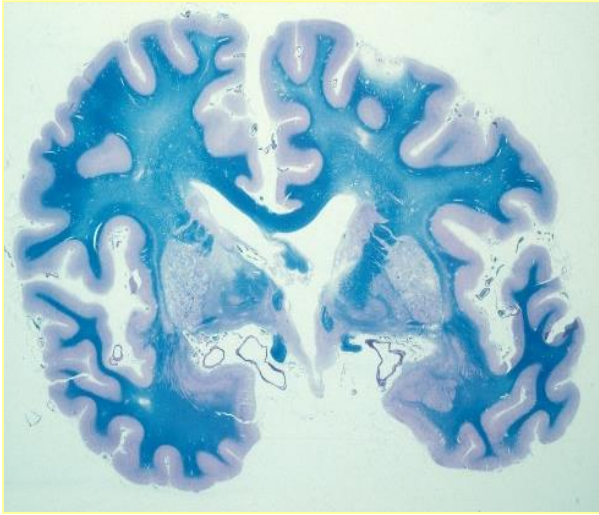
Leukoaraiosis 1987 - 2015

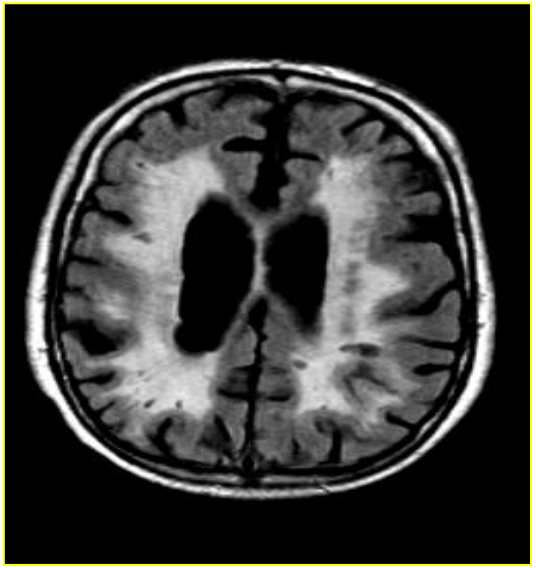
Leuko-Araiosis

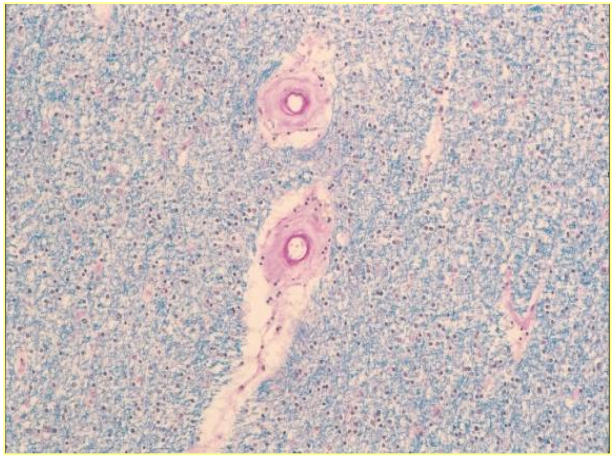
Vladimir C. Hachinski, MD; Paul Potter, MD; Harold Merskey, DM

• Problems in the literature in the appraisal of brain deep white-matter changes are considered. The identification of the changes with Binswanger's disease alone is rejected, and evidence is reviewed that demonstrates that they are associated with cognitive impairment and, to some extent, with vascular disease. Possible causes of white-matter changes and their relationships to Alzheimer's disease are examined, and it is argued that a neutral term, exact enough to define white-matter changes, sufficient as a description or label, and demanding enough to require precise clinical and imaging descriptions is needed. We suggest herein the term "leuko-araiosis" on the basis of Greek etymology and Hippocratic usage.

(*Arch Neurol* 1987;44:21-23)







Leukoaraiosis increases stroke risk

- Consistent results across large hospital based series and population-based studies
- Extensive LA associated with about three times more risk
- Types of stroke predicted mainly lacunar and ICH
- Extensive LA associated with double risk of death and four times risk of dementia

Smith EE, Stroke 2010

Leukoaraiosis and stroke outcome

- Patients with extensive LA fare worse on 3 months Rankin's disability outcome
- LA increases the risk of hemorrhagic transformation of infarct
- LA and infarct volume expansion owing to dysfunctioning microcirculatory collateralization
- LA reduces brain recovery through impaired brain reserve or plasticity
- LA associated with cortical neuronal death
- Quantitative and qualitative white matter dysconnection
- LA is a marker of new ischemic events

Smith EE, Stroke 2010, Henninger N, Stroke 2014

Leukoaraiosis and Sex Predict the Hyperacute Ischemic Core Volume

Nils Henninger, MD; Eugene Lin, MD; Diogo C. Haussen, MD; Laura L. Lehman, MD; Deepak Takhtani, MD; Magdy Selim, MD, PhD; Majaz Moonis, MD

87 patients

Neuroimaging: MR, DWI sequences

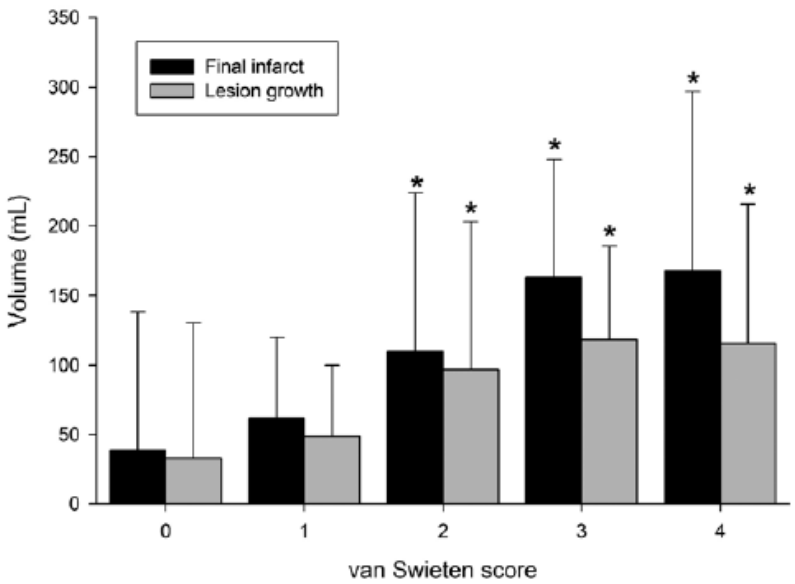


Table 2. Multivariate Logistic Regression Analysis of Factors Independently Associated With a CBV-Lesion Volume of >25 mL

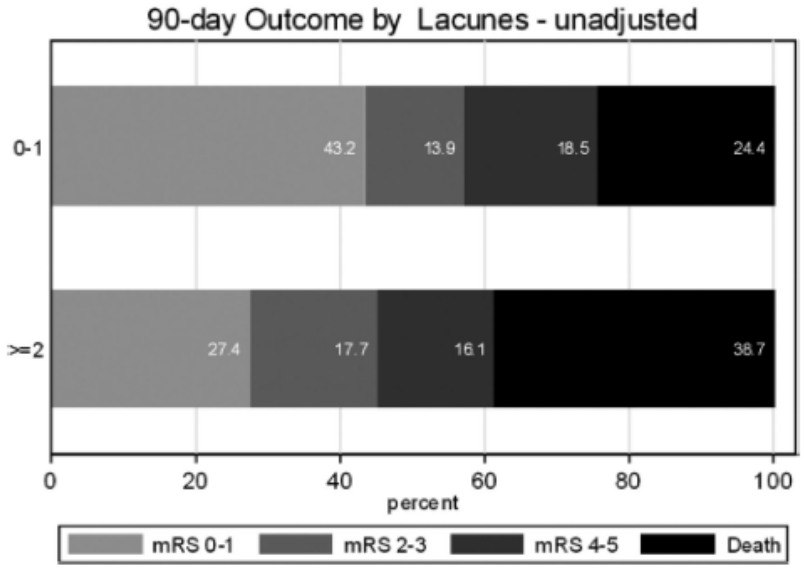
Independent Variable	OR (95% CI)	*P* Value
Age	0.96 (0.90–1.03)	0.242
Male sex	7.52 (1.38–40.86)	0.020
Admission NIHSS	1.12 (0.98–1.27)	0.087
LA grade (VSS 3–4)	43.22 (6.26–298.42)	<0.001
Collateral status (Grade 1–2)	1.93 (0.19–19.96)	0.582
Hypertension	2.25 (0.29–17.39)	0.439
Mean arterial blood pressure, mm Hg	1.01 (0.97–1.04)	0.745
Admission glucose, mg/dL	1.01 (0.99–1.03)	0.287
Admission creatinine, mg/dL	1.12 (0.56–2.40)	0.689

Stroke 2013; 44: 61-67

Leukoaraiosis and intracerebral hemorrhage after thrombolysis in acute stroke

V. Palumbo, MD; J.M. Boulanger, MD, FRCPC; M.D. Hill, MD, FRCPC; D. Inzitari, MD; and A.M. Buchan, MD, FRCP; on behalf of the CASES Investigators*

	VSS > 4 (n = 71), %	VSS ≤ 4 (n = 749), %	Risk difference, %	RR (95% CI)	*p*
sICH	8.4	3.0	5.4	2.75 (1.15–6.53)	0.03
	Lacunes > 2 (n = 70), %	Lacunes ≤ 2 (n = 749), %			
sICH	10	2.9	7.1	3.40 (1.50–7.68)	0.008



RR for death in patients with >=2 lacunes 2.9 (95% CI=1.3-6.2)

Neurology 2007; 68: 1020-1024

Leukoaraiosis and lacunes are associated with poor clinical outcomes in ischemic stroke patients treated with intravenous thrombolysis

Francesco Arba[1], Vanessa Palumbo[2], Jean-Martin Boulanger[3], Giovanni Pracucci[1], Domenico Inzitari[1], Alastair M Buchan[4] and Michael D Hill[5]; on behalf of CASES Investigators

820 patients, Neuroimaging: TC, Severe leukoaraiosis and two or more lacunes considered together in an aggregate score of presence of small vessel disease

- Leukoaraiosis and lacunes reduced chances to have good (mRS 0-2) outcome (OR=0.38; 95% CI=0.20-0.75)
- Leukoaraiosis and lacunes increased risk to have symtpomatic hemorrhage (OR=4.32; 95% CI=2.01-9.30)

Int J Stroke, In Press

Cerebral Computed Tomography-Graded White Matter Lesions Are Associated With Worse Outcome After Thrombolysis in Patients With Stroke

Sami Curtze, MD, PhD; Susanna Melkas, MD, PhD; Gerli Sibolt, MD;
Elena Haapaniemi, MD, PhD; Satu Mustanoja, MD, PhD; Jukka Putaala, MD, PhD;
Tiina Sairanen, MD, PhD; Marjaana Tiainen, MD, PhD; Turgut Tatlisumak, MD, PhD;
Daniel Strbian, MD, PhD

2485 pts, Neuroimaging: TC, 4 visual scales for white matter lesions

All the 4 visual scales associated with worse outcomes at all binary levels and in shift analysis of the modified Rankin Scale

Stroke 2015; 46: 2149-2155

White Matter Lesions Double the Risk of Post-Thrombolytic Intracerebral Hemorrhage

Sami Curtze, MD, PhD; Elena Haapaniemi, MD, PhD; Susanna Melkas, MD, PhD; Satu Mustanoja, MD, PhD; Jukka Putaala, MD, PhD; Tiina Sairanen, MD, PhD; Gerli Sibolt, MD; Marjaana Tiainen, MD, PhD; Turgut Tatlisumak, MD, PhD; Daniel Strbian, MD, PhD

2485 pazienti

Neuroimaging: TC

4 visual scales for white matter lesions

- All the 4 visual scales were associated with worse outcomes of the modified Rankin Scale and with a more than two-fold risk of sICH
- High load of white matter lesions was associated with remote hemorrhage (OR=4.11; 95% CI=2.38-7.10)

Stroke 2008; 39: 1409-1413

Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial

3017 pts., Neuroimaging: TC

Leukoaraiosis reduced chances to be independent (OHS) 6 months after the stroke index event (OR=0.72; 95% CI=0.59-0.87)

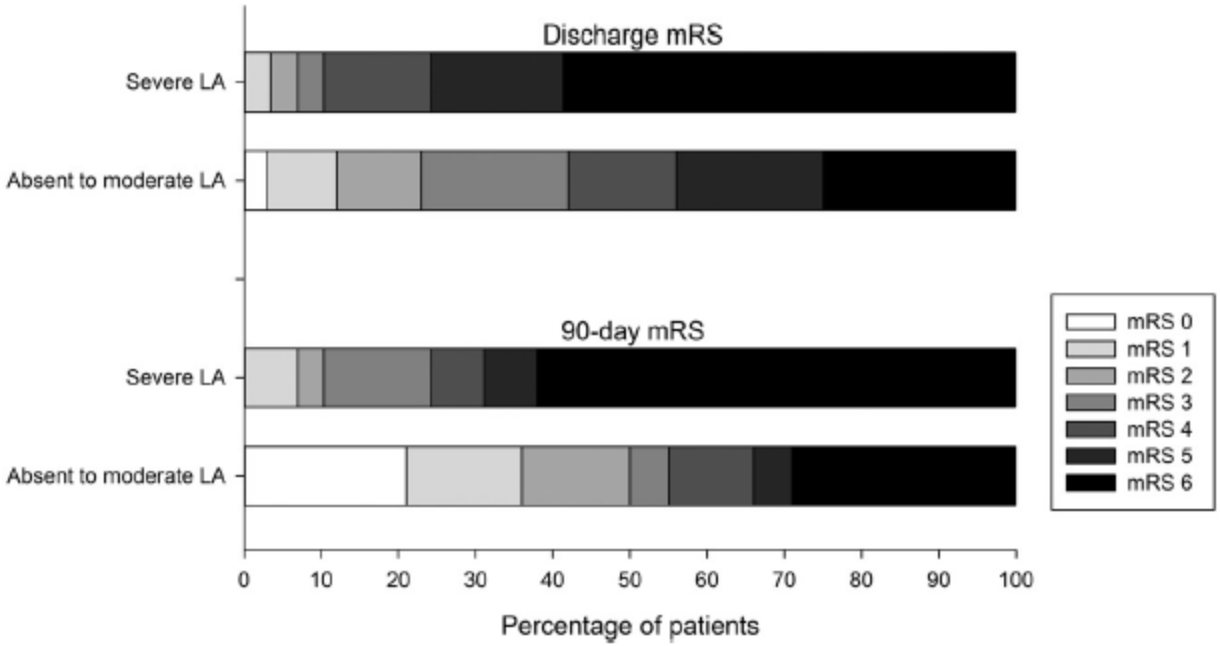
Lancet Neurol 2015; 14: 485-496

Leukoaraiosis Predicts a Poor 90-Day Outcome after Endovascular Stroke Therapy

J. Zhang, A.S. Puri, M.A. Khan, R.P. Goddeau Jr, and N. Henninger

- Severe leukoaraiosis was independently associated with poor (mRS 3-6) outcome

(OR=6.03; 95% CI=1.80-22.11)



AJNR 2014; 35: 2070-2075

Conclusioni

- Trombolisi efficace anche negli ultraottantenni solo se effettuata entro 3 ore dall'inizio dei sintomi
- Trattamento endovascolare anche efficace con i criteri di selezione dei trial e delle linee guida
- Trombectomia meccanica teoricamente molto efficace nello stroke ischemico associato ad FA, ma dati per ora inconclusivi
- Trombolisi teoricamente efficace in pazienti con disabilità pre-ictus, ma evidenza non controllata
- Leukoaraiosi estesa determinante potenzialmente negativo per qualsiasi tipo di trattamento