

Relevancia de los defectos de perfusión persistentes tras la recanalización en el ictus de gran vaso.

Ensayo clínico — CHOICE²

Xabier Urra, Sergio Amaro, Laura Lull, Valérie Petegnief, Carles Justícia, Víctor Obach, Alejandro Vázquez, Martha Vargas, Anna Planas, Arturo Renú, Ángel Chamorro; en nombre de los colaboradores de CHOICE-2



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Microcirculación en el ictus de gran vaso

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Ensayo  CHOICE

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Ensayo  CHOICE-2

Alteración de la microcirculación en isquemia cerebral experimental

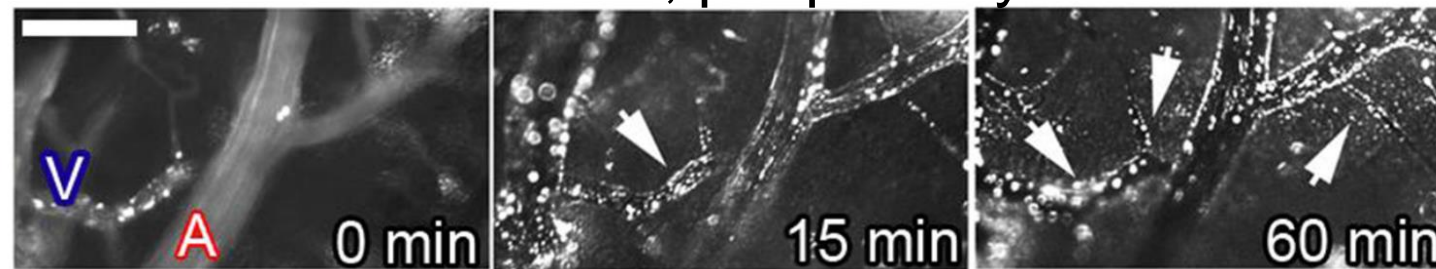
1968

Cerebral Ischemia

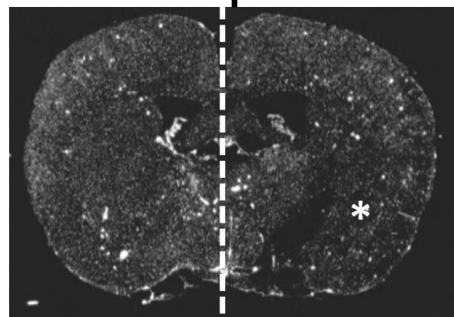
II. The No-Reflow Phenomenon → ¿Espasmo?

Adelbert Ames III, M.D., R. Lewis Wright, M.D., Masayoshi Kowada, M.D., Jean M. Thurston, A.B., and Guido Majno, M.D.

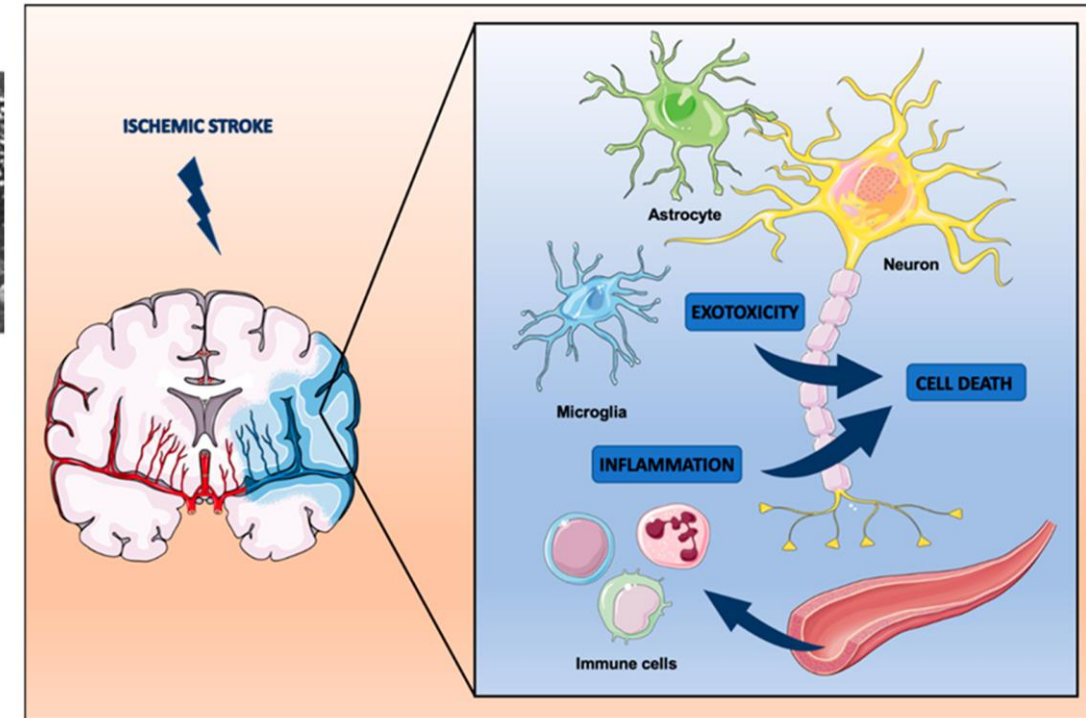
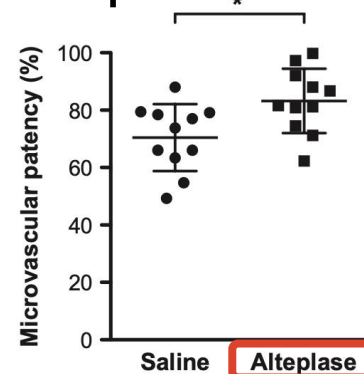
Acúmulo de fibrina, plaquetas y leucocitos



Responde a alteplasa



Left hemisphere Right hemisphere

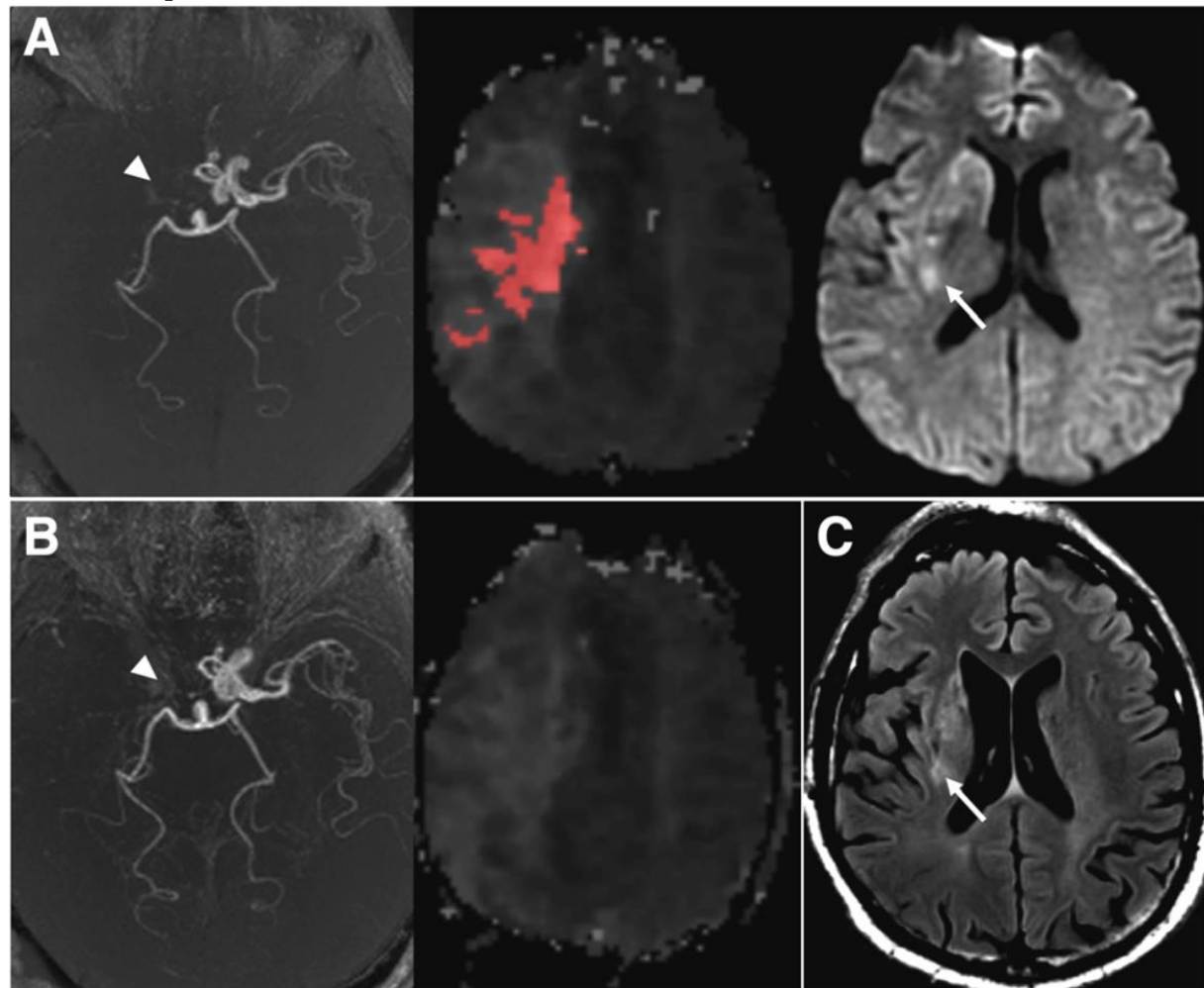


Haupt M, et al. Int J Mol Sci 2022

Desilles JP, et al. Stroke 2015

Relevancia clínica de la hipoperfusión


Reperfusion ≠ Recanalización



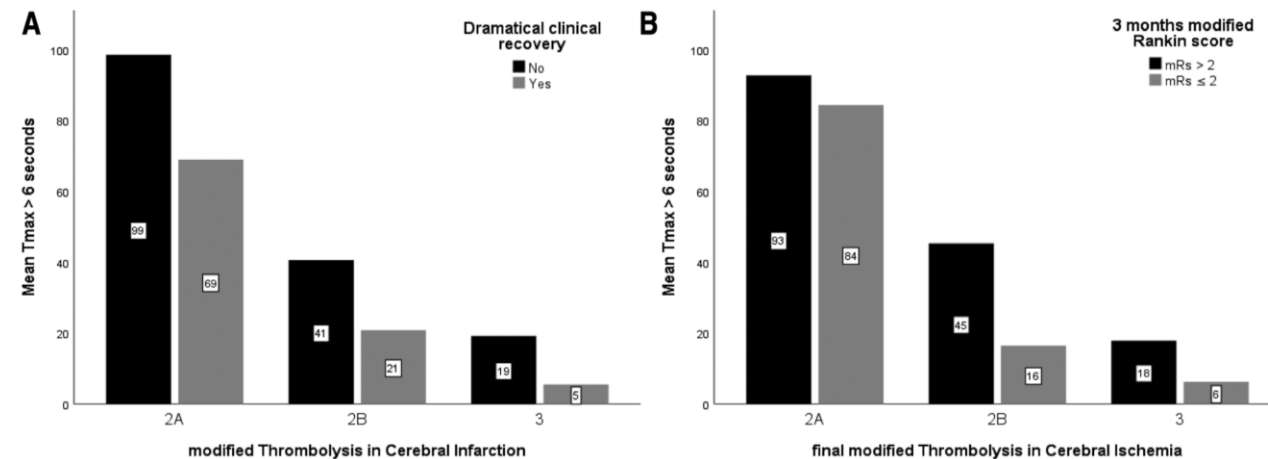
Cho TH, et al. Stroke 2015

Stroke 2020

Computed Tomography Perfusion After Thrombectomy An Immediate Surrogate Marker of Outcome After Recanalization in Acute Stroke

Marta Rubiera , MD; Alvaro Garcia-Tornel, MD;
Marta Olivé-Gadea, MD; Daniel Campos, MD; Manuel Requena, MD; Carla Vert, MD;
Jorge Pagola, MD; David Rodriguez-Luna, MD; Marian Muchada, MD; Sandra Boned, MD;
Noelia Rodriguez-Villatoro, MD; Jesus Juega, MD; Matias Deck, MD; Estela Sanjuan, PhD;
David Hernandez, MD; Carlos Piñana, MD; Alejandro Tomasello, MD; Carlos A. Molina, MD;
Marc Ribo, MD

Efectos deletéreos de la hipoperfusión post-TM



Empleo ocasional de trombolisis IA

Encuesta EEUU: 60%

Castonguay AC, et al. Front Neurol 2019

How often do you use IA thrombolytic for treatment for acute ischemic stroke?

Never (41/104; 39.4%)

1–5 cases per year (49/104; 47.1%)

6–10 cases per year (6/104; 5.8%)

11–20 cases per year (4/104; 3.8%)

>20 cases per year (4/104; 3.8%)

Guías AHA Tratamiento agudo del ictus 2019

Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be **reasonable** to achieve mTICI grade 2b/3 angiographic results.

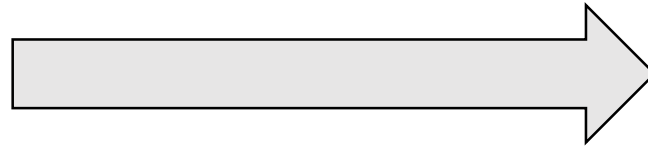
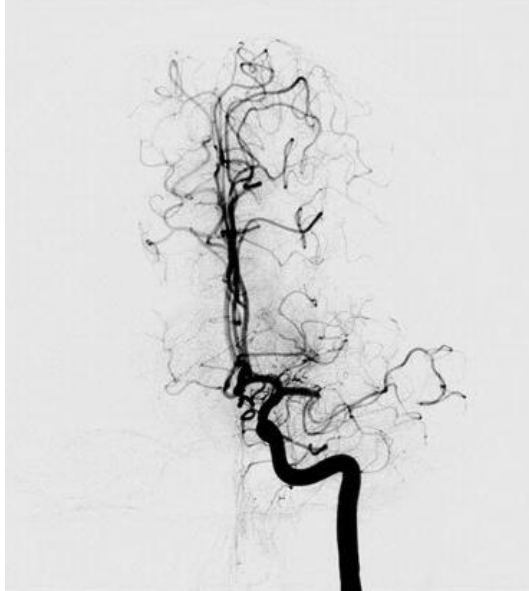
IIb

C-LD

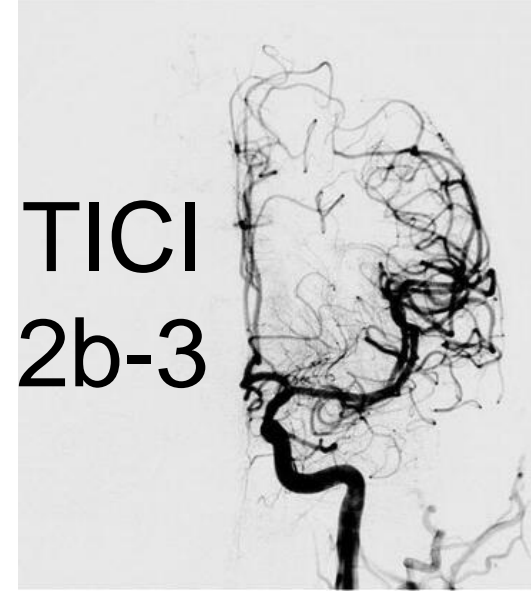
La Marató



CHOICE



TICI
2b-3

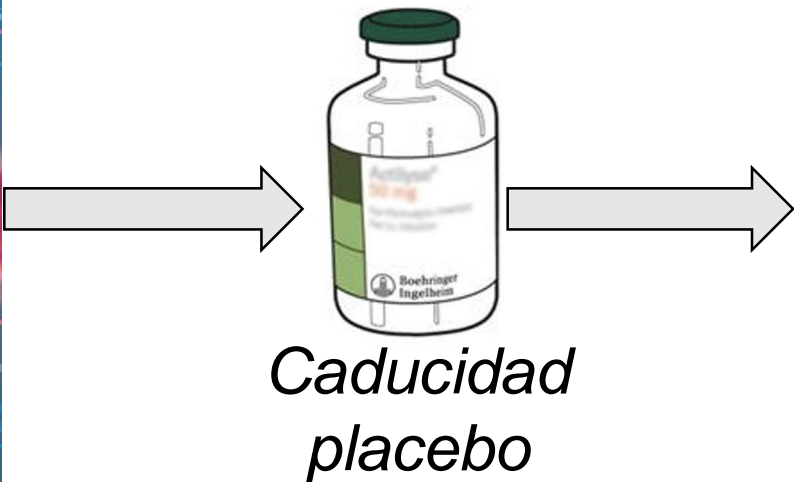


JAMA 2022



**Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke
The CHOICE Randomized Clinical Trial**

Arturo Renú, MD; Mónica Millán, MD; Luis San Román, MD; Jordi Blasco, MD; Joan Martí-Fàbregas, MD; Mikel Terceño, MD; Sergio Amaro, MD; Joaquín Serena, MD; Xabier Urrea, MD; Carlos Laredo, PhD; Roger Barranco, MD; Pol Camps-Renom, MD; Federico Zarco, MD; Laura Oleaga, MD; Pere Cardona, MD; Carlos Castaño, MD; Juan Macho, MD; Elisa Cuadrado-Godía, MD; Elio Vivas, MD; Antonio López-Rueda, MD; Leopoldo Guimaraens, MD; Anna Ramos-Pachón, MD; Jaume Roquer, MD; Marian Muchada, MD; Alejandro Tomasello, MD; Antonio Dávalos, MD; Ferran Torres, MD; Ángel Chamorro, MD; for the CHOICE Investigators

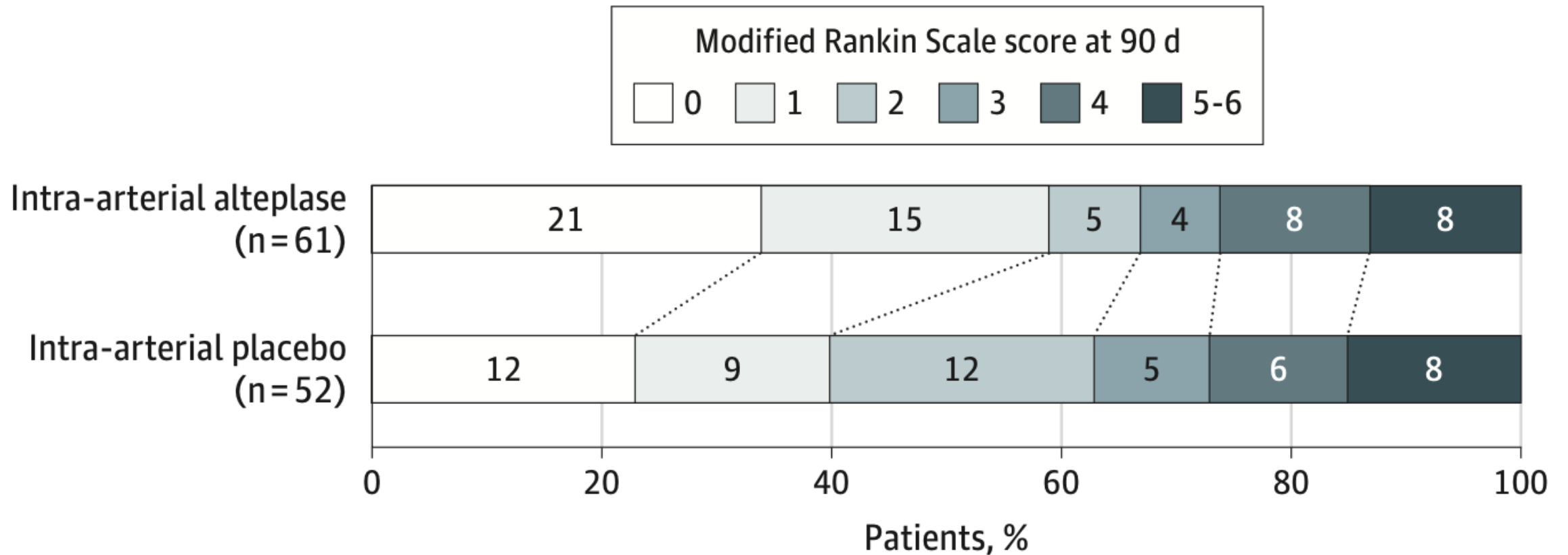


STOP tras reclutar
60%
(200 previstos)

Alteplasa IA fue segura

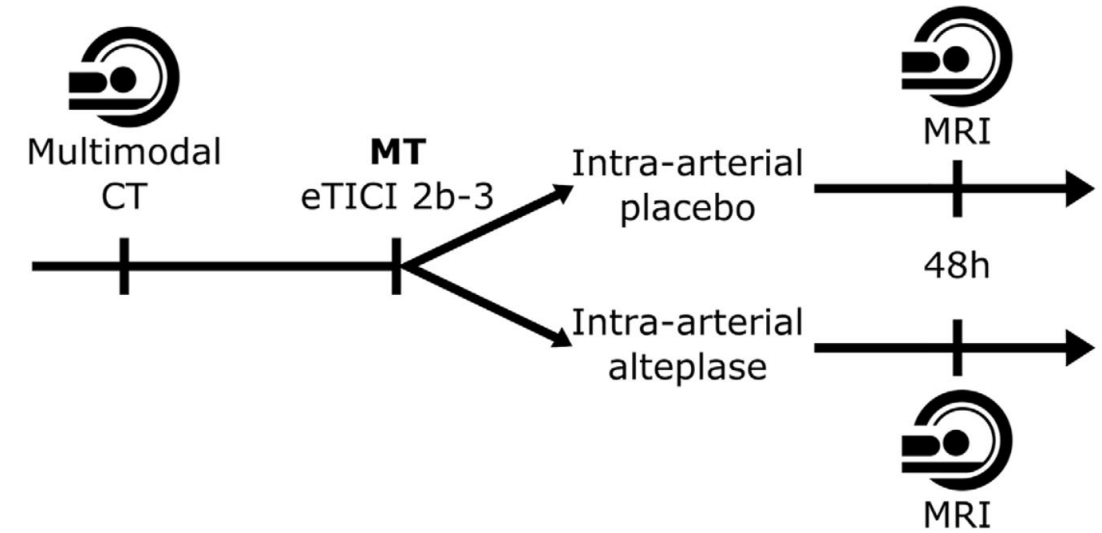
Outcomes	No. (%) of participants	
	Alteplase (n = 61)	Placebo (n = 52)
Primary safety outcomes		
Symptomatic intracranial hemorrhage at 24 h	0	2 (3.8)
Death at 90 d	5 (8.2)	8 (15.4)

Alteplasa IA mejoró el pronóstico funcional




Outcomes	Alteplase (n = 61)	Placebo (n = 52)	Absolute risk difference, % (95% CI)	P value ^a
Primary outcome				
Score of 0 or 1 on modified Rankin Scale at 90 d, No. (%)	36 (59.0)	21 (40.4)	18.4 (0.3 to 36.4)	.047

Subestudio de imagen: mecanismos implicados



Ann Neurol 2022

Adjunct Thrombolysis Enhances Brain Reperfusion following Successful Thrombectomy

Carlos Laredo, PhD,^{1†} Alejandro Rodríguez, MD,^{2†} Laura Oleaga, MD,³
María Hernández-Pérez, MD,⁴ Arturo Renú, MD,^{1,2} Josep Puig, MD,⁵
Luis San Román, MD,³ Anna M. Planas, PhD,^{1,6} Xabier Urra, MD,^{1,2,7} and
Ángel Chamorro, MD ^{1,2,7}

Alteplasa IA redujo la hipoperfusión y limitó la expansión del infarto

Intra-Arterial Alteplase, n = 17

Intra-Arterial Placebo, n = 19

p

Angiographic improvement, n (%)

0

3 (16%)

0.09

Abnormal perfusion at 48 hours, n (%)

4 (24%)

11 (58%)

0.03

TMAX > 6 volume, median (IQR)

0

0.76 (0.07–2.33)

0.04

Expanding infarction, n (%)

6 (35%)

14 (74%)

0.02

Infarct expansion ratio, median (IQR)

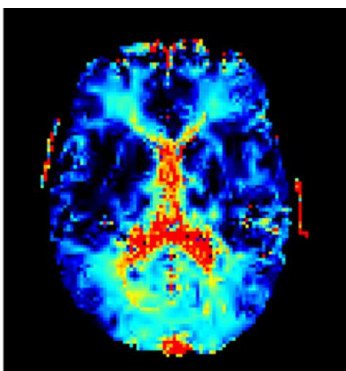
0.79 (0.50–1.44)

3.23 (1.79–5.73)

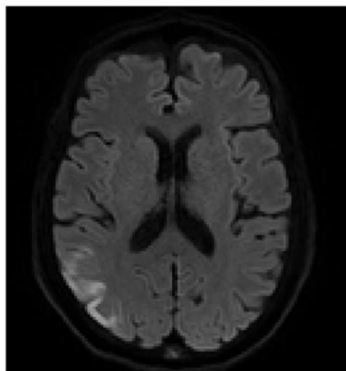
0.02

ALTEPLASA

- PWI TMAX > 6s vol = 0 mL



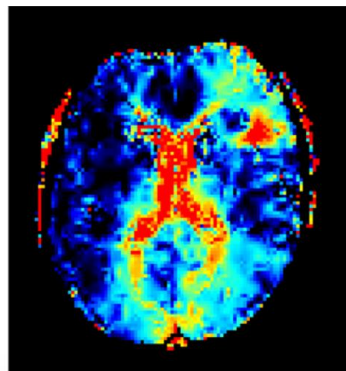
PWI TMAX



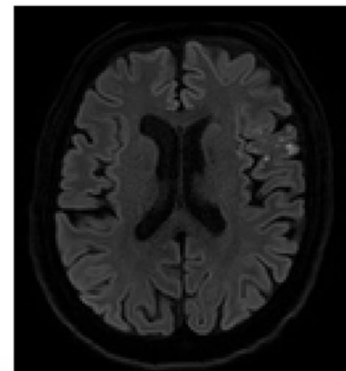
DWI

PLACEBO

- PWI TMAX > 6s vol = 3 mL

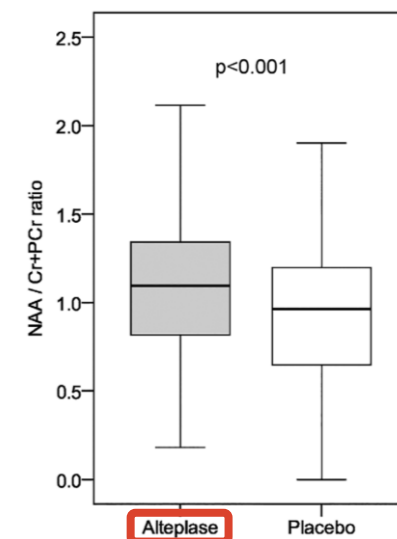


PWI TMAX



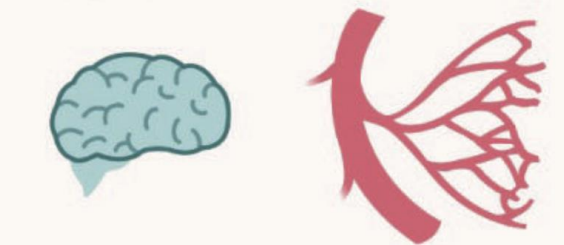
DWI

Mayores picos de NAA (integridad neuronal)

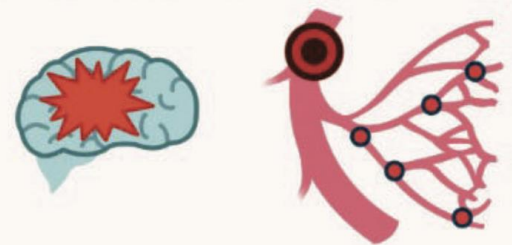




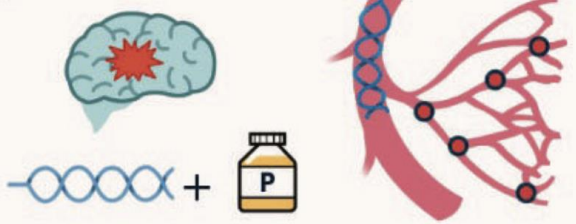
1. Healthy brain



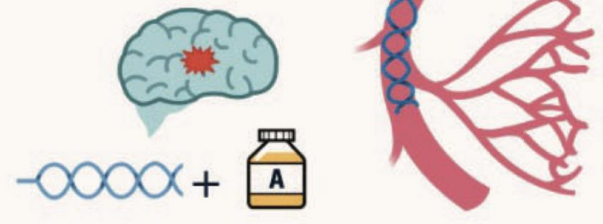
2. Brain with Acute Ischemic Stroke (AIS)



3. Brain with AIS treated with mechanical thrombectomy + placebo (P)



4. Brain with AIS treated with mechanical thrombectomy + Alteplase (A)



LIMITACIÓN

nº pacientes

CHOICE-2



Academic Clinical Trials Call. Proposal Application Form

OBJETIVO

Confirmar si la administración intra-arterial de trombólisis tras una trombectomía angiográficamente exitosa mejora el resultado funcional de los pacientes con ictus isquémico por oclusión de gran vaso

CHOICE-2

Diseño

N = 440

14% diferencia

- Clínic Barcelona *Arturo Renú*
- Santa Creu i Sant Pau *Pol Camps*
- Mar *Elisa Cuadrado*
- Josep Trueta *Mikel Terceño*
- Germans Trias i Pujol *Laura Dorado*
- A Coruña *María Dolores Fernández*
- Donostia *Maitane Alonso*
- Cruces *María del Mar Freijo*
- La Fe *José Tembl*
- Virgen de la Arrixaca *Ana Morales*
- Valladolid *Juan Francisco Arenillas*
- Central de Asturias *Pedro Vega*



POPULATION

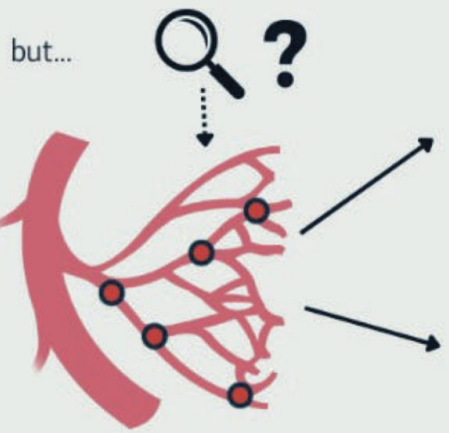
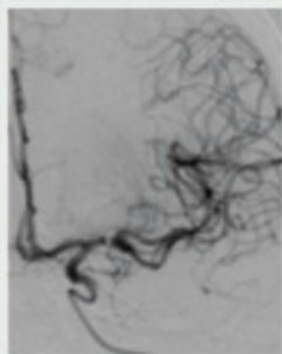
Adults with large vessel occlusion acute ischemic stroke successfully treated with thrombectomy

LOCATION

12 stroke centers in Spain



Normal angiography post-thrombectomy



but...

ALTEPLASE

Intra-arterial alteplase, 0.225 mg/kg, infused over 10 minutes.

PLACEBO

Intra-arterial placebo infused over 10 minutes.



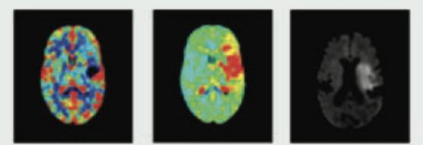
Randomization 1:1

PRIMARY OUTCOME

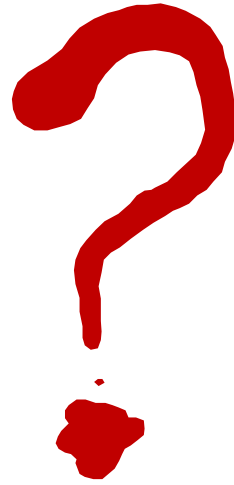
Modified Rankin Scale 0-1 at 90 days.

SECONDARY OUTCOME

Microvascular hypoperfusion on imaging at 48 hours.



Escasez mundial de alteplasa



23 September 2022
EMA/734545/2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

**Shortage of Actilyse (alteplase)
10, 20 and 50 mg powder and solvent for solution for injection and infusion**

THE LANCET
Neurology

CORRESPONDENCE | VOLUME 400, ISSUE 10359, P1193-1194, OCTOBER 08, 2022
Protecting patients during a shortage of thrombolytic agents
Fionnuala Ní Áinle ✉ • Saskia Middeldorp • Grégoire Le Gal • Beverley J Hunt

CORRESPONDENCE | VOLUME 22, ISSUE 1, P28, JANUARY 2023
The shortage of thrombolytics for stroke: a call for action
Umberto Pensato ✉ • Michele Romoli • Serena Marita Lazzarin • Simona Marcheselli • Andrea Zini

CHOICE² Diseño PROBE

Alteplasa IA vs. No alteplasa IA

Evaluación ciega:

- Outcome primario: reperusión
- mRS 3 meses centralizado

Conclusiones

La microcirculación es crucial en el daño cerebral isquémico causado por oclusión de un gran vaso

La hipoperfusión persistente es frecuente incluso tras la recanalización angiográficamente satisfactoria, y la administración IA de alteplasa la minimiza

Esperamos confirmar en CHOICE-2 el beneficio clínico de la alteplasa IA para incorporarla a las guías terapéuticas del ictus con el grado máximo de evidencia

Gracias

CHOICE-2



Ángel Chamorro
Group leader (R4)

Enfermedades cerebrovasculares



Josep Juan González
Accredited researcher (R3A)



Laura Llull
Accredited researcher (R3A)



Mattia Gallizioli
Post-doctoral researcher (R2A)



Carlos Laredo
Post-doctoral researcher (R2A)



Alejandro Rodríguez-Vázquez
Pre-doctoral researcher (R1)



Daniel Santana Moreno
Pre-doctoral researcher (R1)



Arturo Renú
Accredited researcher (R3A)



Ramon Torné
Accredited researcher (R3A)



Jordi Pedragosa
Post-doctoral researcher (R2A)



Leire Pedrosa
Post-doctoral researcher (R2A)



Leonardo Marquez
Technician



Francisca Ruiz
Technician



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Martha Elena Vargas
Administrative staff



Mònica Serrano
Nursing staff

