Microsesiones

Doble antiagregación vs alteplasa en ictus minor: evidencia reciente

Juan Alcalá Torres

DOBLE ANTIAGREGACIÓN VS ALTEPLASA: LO QUE SABEMOS

- Ictus minor (NIHSS <5): 50% del total de ictus isquémicos.
- En ictus minor no discapacitantes, alteplasa no mejora pronóstico a los 90 días, pero sí confiere un mayor riesgo hemorrágico (PRISMS).
- Dos estudios confirman eficacia y seguridad de DA en las primeras 12-24h en ictus minor y AIT (alto riesgo) (POINT y CHANCE).
- Beneficio en evitar la recurrencia de ictus máximo las primeras 2 semanas (CHANCE).
- ¿Es DA no inferior a alteplasa en pacientes con ictus minor no discapacitantes? ¿Menor riesgo hemorrágico?

Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS) study

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June 27, 2023

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The ARAMIS Randomized Clinical Trial

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Métodos:

- Ensayo clínico multicéntrico (38 hospitales en China) randomizado 1:1, no inferioridad.
- DA comparada con alteplasa en las primeras 4,5 horas.
- Criterios de inclusión: Pacientes adultos, ictus minor no discapaciante, NIHSS ≤ 5, TC o RM.
- Criterios de exclusión: mRS ≥ 2, hemorragia cerebral, indicación de anticoagulación.
- Protocolo: dosis de carga de clopidogrel (300mg → 75mg) + AAS (sin dosis de carga, 100mg).
  - Mantenimiento de DA entre 12-90 días (según indicación) → antiagreg simple.
- Outcome primario: mRS 90 días (0-1),
- Outcome secundarios: mRS 90 días (0-2), cambio NIHSS en primeras 24h (± 2), reictus a los 90 días, mortalidad a los 90 días, hemorragia intracraneal sintomática (NIHSS >4), cualquier sangrado sistémico.
- Estudio de cálculo muestral
- Estudio estadístico: límite de no inferioridad en -4,5%, p <0,05

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- **<u>Resultados</u>**: 760 pacientes (393 DA, 367 alteplasa).
  - 147 desv protocolo (cambio DA por alteplasa y viceversa).
  - Análisis por protocolo e intención de trarar resultados similares.
- Edad media: 64 años (57-71). Sexo: 31% mujeres.
- NIHSS medio: 2 (1-3).
- Mediana de tiempo ictus-tratamiento: 182min (133-230) DA vs 180min (126-225) alteplasa.
- 33,7% no estudio vascular.

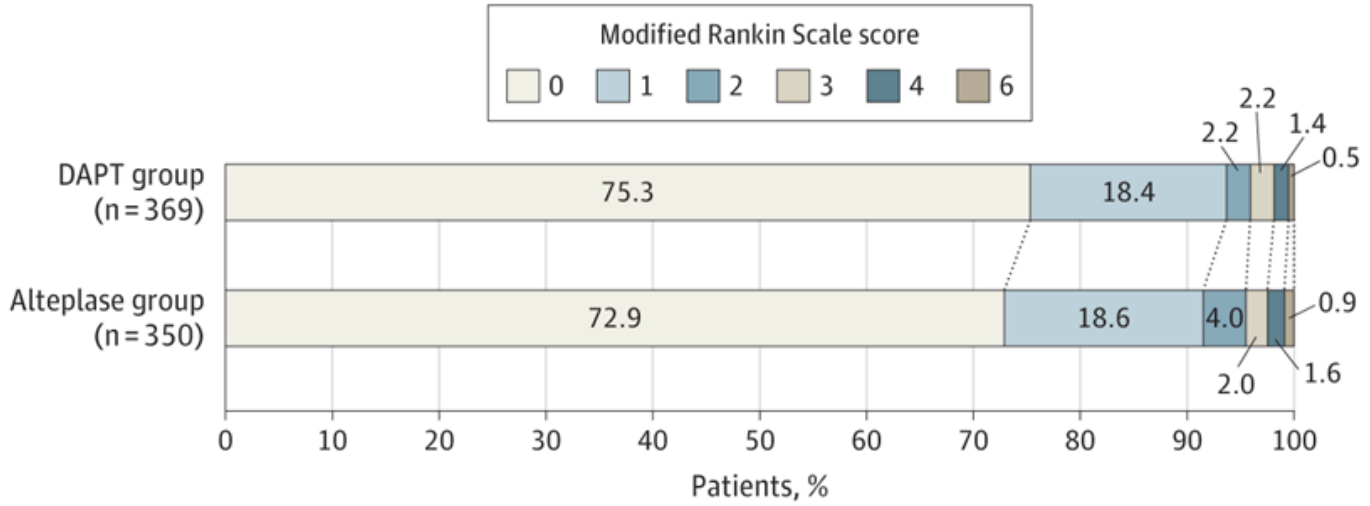
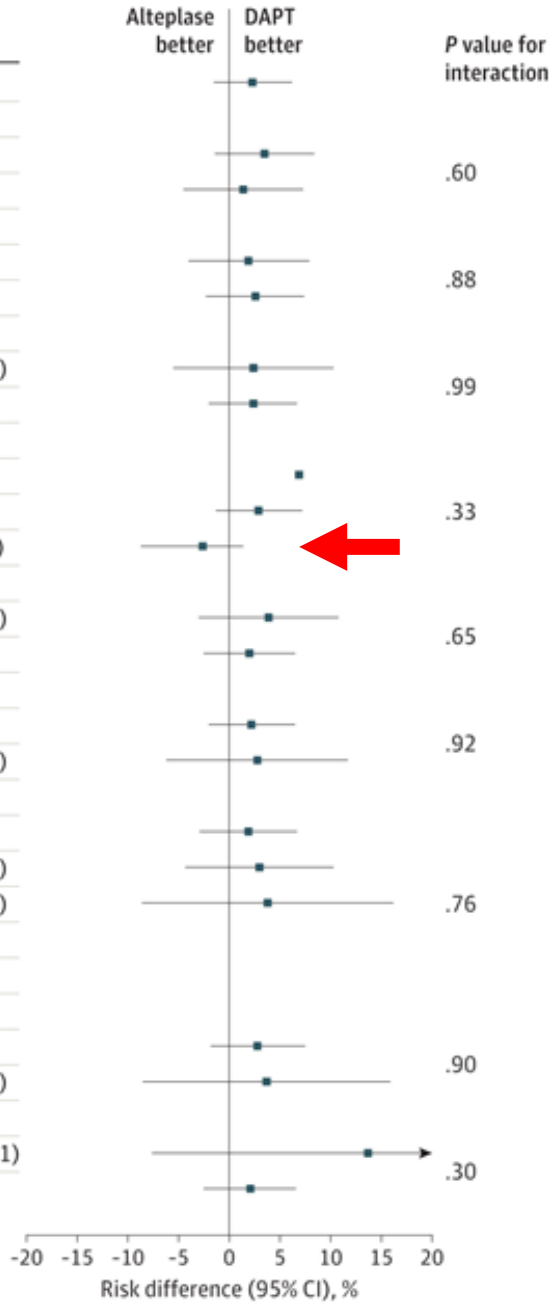


Table 2. Trial Outcomes in the Full Analysis Set and Safety Population

Outcome	No. (%)		Unadjusted			Adjusted[a]	
	Dual antiplatelet treatment (n = 369)	Alteplase (n = 350)	Treatment effect metric	Treatment difference (95% CI)	*P* value	Treatment difference (95% CI)	*P* value
Primary outcome (full analysis set)							
mRS score 0-1 within 90 d[b]	346 (93.8)	320 (91.4)	Risk difference[c,d]	2.3% (−1.5% to 6.2%)	<.001	2.3% (−1.6% to 6.1%)	<.001
			Risk ratio[c]	1.38 (0.81 to 2.32)	.23	1.36 (0.80 to 2.30)	.22
Secondary outcomes (full analysis set)							
mRS score 0-2 within 90 d[b]	354 (95.9)	334 (95.4)	Risk difference[c]	0.5% (−2.5% to 3.5%)	.74	0.5% (−3.5% to 2.5%)	.83
			Risk ratio[c]	1.12 (0.56 to 2.24)	.74	1.12 (0.56 to 2.25)	.64
mRS score distribution within 90 d[b]			Odds ratio[c]	1.16 (0.83 to 1.61)	.39	1.11 (0.80 to 1.55)	.51
Early neurological improvement within 24 h[e]	62 (16.8)	74 (21.1)	Risk difference[c]	−4.1% (−9.8% to 1.7%)	.16	−3.1% (−8.7% to 2.4%)	.27
			Risk ratio[c]	0.95 (0.89 to 1.02)	.17	0.84 (0.62 to 1.14)	.27
Early neurological deterioration within 24 h[f]	17 (4.6)	32 (9.1)	Risk difference[c]	−4.5% (−8.2% to −0.8%)	.02	−4.6% (−8.3% to −0.9%)	.02
			Risk ratio[c]	0.50 (0.29 to 0.89)	.02	0.50 (0.28 to 0.89)	.02
Median change in NIHSS score at 24 h from baseline[g]	0 (−0.41 to 0)	0 (−0.69 to 0)	Geometric mean ratio[c]	0.03 (−0.05 to 0.11)	.51	0.01 (−0.07 to 0.09)	.68
Stroke or other vascular events within 90 d	1 (0.3)	2 (0.6)	Hazard ratio[h]	0.47 (0.04 to 5.20)	.54	0.46 (0.04 to 5.17)	.45
Death at 90 d	2 (0.5)	3 (0.9)	Risk difference[c]	−0.3% (−1.5% to 0.9%)	.61	−0.3% (−1.5% to 0.9%)	.49
			Risk ratio[c]	0.63 (0.11 to 3.76)	.61	0.58 (0.10 to 3.51)	.49
Safety outcomes (safety population)							
Symptomatic intracerebral hemorrhage[i]	1/371 (0.3)	3/352 (0.9)	Risk difference[c]	−0.6% (−1.7% to 0.5%)	.30	−2.4% (−12.1% to 7.3%)	.63
			Risk ratio[c]	0.32 (0.03 to 3.02)	.32	0.31 (0.03 to 2.99)	.36
Any bleeding events[j]	6/371 (1.6)	19/352 (5.4)	Risk difference[c]	−3.8% (−6.5% to −1.1%)	.006	−3.6% (−6.4% to −0.7%)	.01
			Risk ratio[c]	0.30 (0.12 to 0.74)	.009	0.31 (0.12 to 0.76)	.01

Subgroup	No. of patients	No. of patients with primary outcome/total No. (%)		Risk difference (95% CI), %	*P* value for interaction
		DAPT group	Alteplase group		
Overall	719	346/369 (93.8)	320/350 (91.4)	2.3 (-1.5 to 6.2)	
Age, y					
<65	366	170/178 (95.5)	173/188 (92.0)	3.5 (-1.4 to 8.4)	.60
≥65	353	176/191 (92.1)	147/162 (90.7)	1.4 (-4.5 to 7.3)	
Sex					
Women	223	108/113 (95.6)	103/110 (93.6)	1.9 (-4.0 to 7.9)	.88
Men	496	238/256 (93.0)	217/240 (90.4)	2.6 (-2.3 to 7.4)	
History of diabetes					
Yes	187	94/101 (93.1)	78/86 (90. 7)	2.4 (-5.5 to 10.3)	.99
No	532	252/268 (94.0)	242/264 (91.7)	2.4 (-2.0 to 6.7)	
NIHSS score at admission					
0	56	27/27 (100.0)	27/29 (93.1)	6.9	
1-3	529	264/278 (95.0)	231/251 (92.0)	2.9 (-1.3 to 7.2)	.33
4-5	134	55/64 (85.9)	62/70 (88.6)	-2.6 (-8.7 to 1.4)	
Time from symptom onset to treatment, h					
≤2	145	69/71 (97.2)	69/74 (93.2)	3.9 (-3.0 to 10.8)	.65
>2	574	277/298 (93.0)	251/276 (90.9)	2.0 (-2.5 to 6.5)	
Location of responsible vessel					
Anterior circulation stroke	562	266/283 (94.0)	256/279 (91.8)	2.2 (-2.0 to 6.5)	.92
Posterior circulation stroke	153	77/83 (92.8)	63/70 (90.0)	2.8 (-6.2 to 11.7)	
Stroke etiology					
Undetermined cause	446	221/225 (93.8)	203/221 (91.9)	1.9 (-2.9 to 6.7)	
Small artery occlusion	166	83/87 (95.4)	73/79 (92.4)	3.0 (-4.3 to 10.3)	
Large artery arteriosclerosis	100	49/54 (90.7)	40/46 (87.0)	3.8 (-8.6 to 16.2)	.76
Other determined cause	5	2/2 (100.0)	3/3 (100.0)		
Cardioembolic	2	1/1 (100.0)	1/1 (100.0)		
Degree of responsible vessel stenosis, %					
50	375	182/190 (95.8)	172/185 (93.0)	2.8 (-1.8 to 7.5)	.90
>50	102	50/55 (90.9)	41/47 (87.2)	3.7 (-8.5 to 15.9)	
Large artery occlusion					
Yes	36	19/20 (95.0)	13/16 (81.3)	13.7 (-7.6 to 35.1)	.30
No	441	213/225 (94.7)	200/216 (92.6)	2.1 (-2.5 to 6.6)	



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Limitaciones:

- Estudio de no inferioridad → no se puede establecer como un tratamiento estándar.
- Guías actuales AHA 2021 y ESO 2021 no incluyen la DA como tratamiento en primeras 4,5h (sí en las primeras 24h)
- Desviaciones del protocolo 20,4% (147: 87 DA→ Alt // 60 Alt → DA).
  - Estudios por intención de tratar y por protocolo arrojan resultados similares.
- No estudio vascular 33,7% (¿estenosis intracraneal / oclusión de gran vaso?).
- Ictus con NIHSS 4-5 → ¿posible superioridad de alteplasa?
- Evaluadores ciegos, pero neurólogos que reevalúan a los pacientes no ciegos
- Exclusión de pacientes con causa cardioembólica
- Minoría de mujeres. Población asiática.
- Resultados “demasiado” buenos en ambos grupos respecto a la literatura previa.

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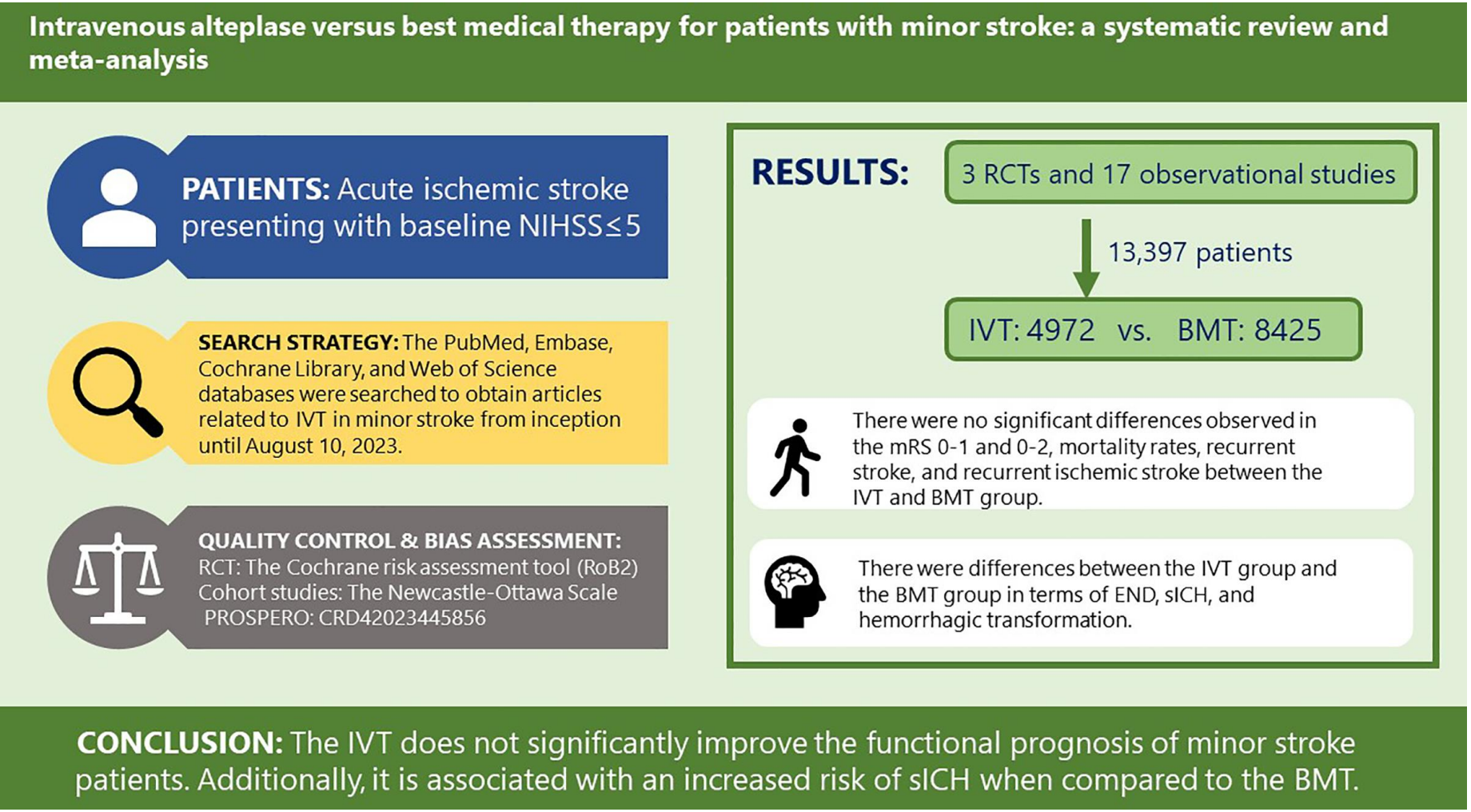
Conclusiones:

- La DA es no inferior a alteplasa en pacientes con ictus minor no discapacitante en las primeras 4,5 horas.
- Menor perfil de hemorragias intracraneales o eventos hemorrágicos.

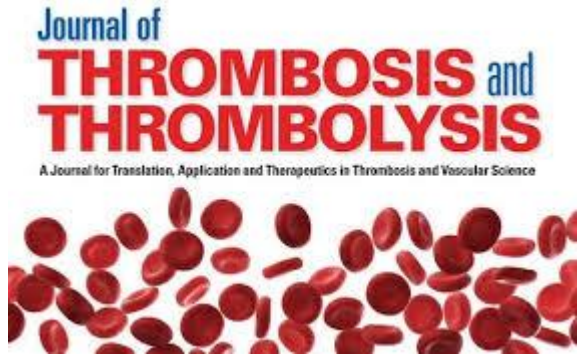
RÉPLICAS A ESTE ESTUDIO

Stroke



- FiV no implica una mejoría significativa en el pronóstico de los ictus minor respecto al mejor tratamiento médico (MTM)
- Aumento de riesgo de hemorragia intracraneal respecto al MTM.
- FiV puede no ser superior al MTM en ictus minor no discapacitantes.

RÉPLICAS A ESTE ESTUDIO



Dual Antiplatelet Therapy vs Alteplase in Adult Patients with Acute Minor Ischemic Stroke: A Systematic Review and Meta-Analysis

Design and Methods

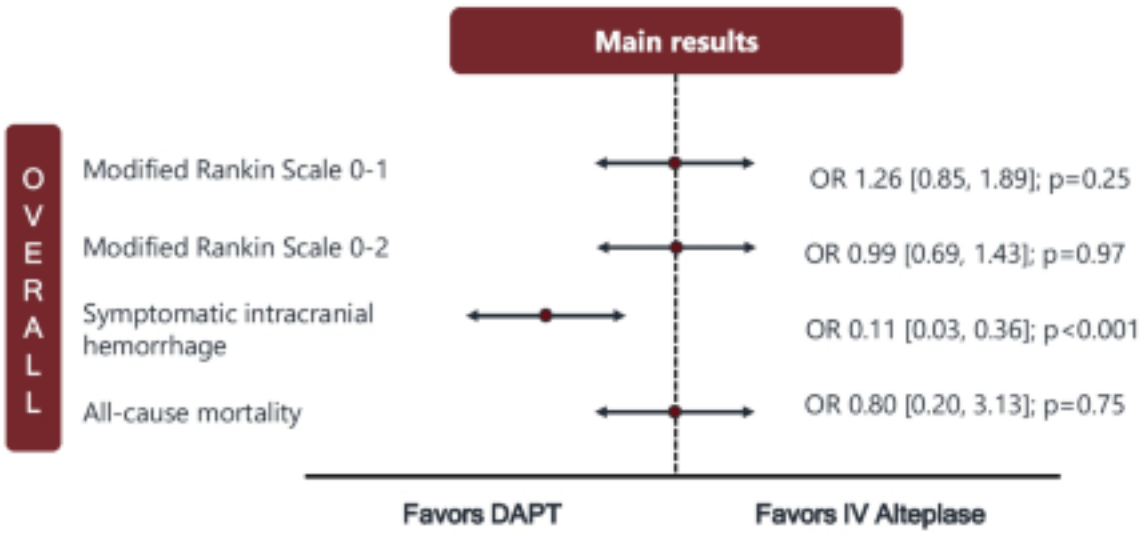
Studies comparing dual antiplatelet therapy (DAPT) with IV Alteplase in adult patients with acute minor ischemic stroke

5 studies (1 RCT and 5 observational) were included

6,340 patients

♂ 69.6% 64.9% DAPT

Main results



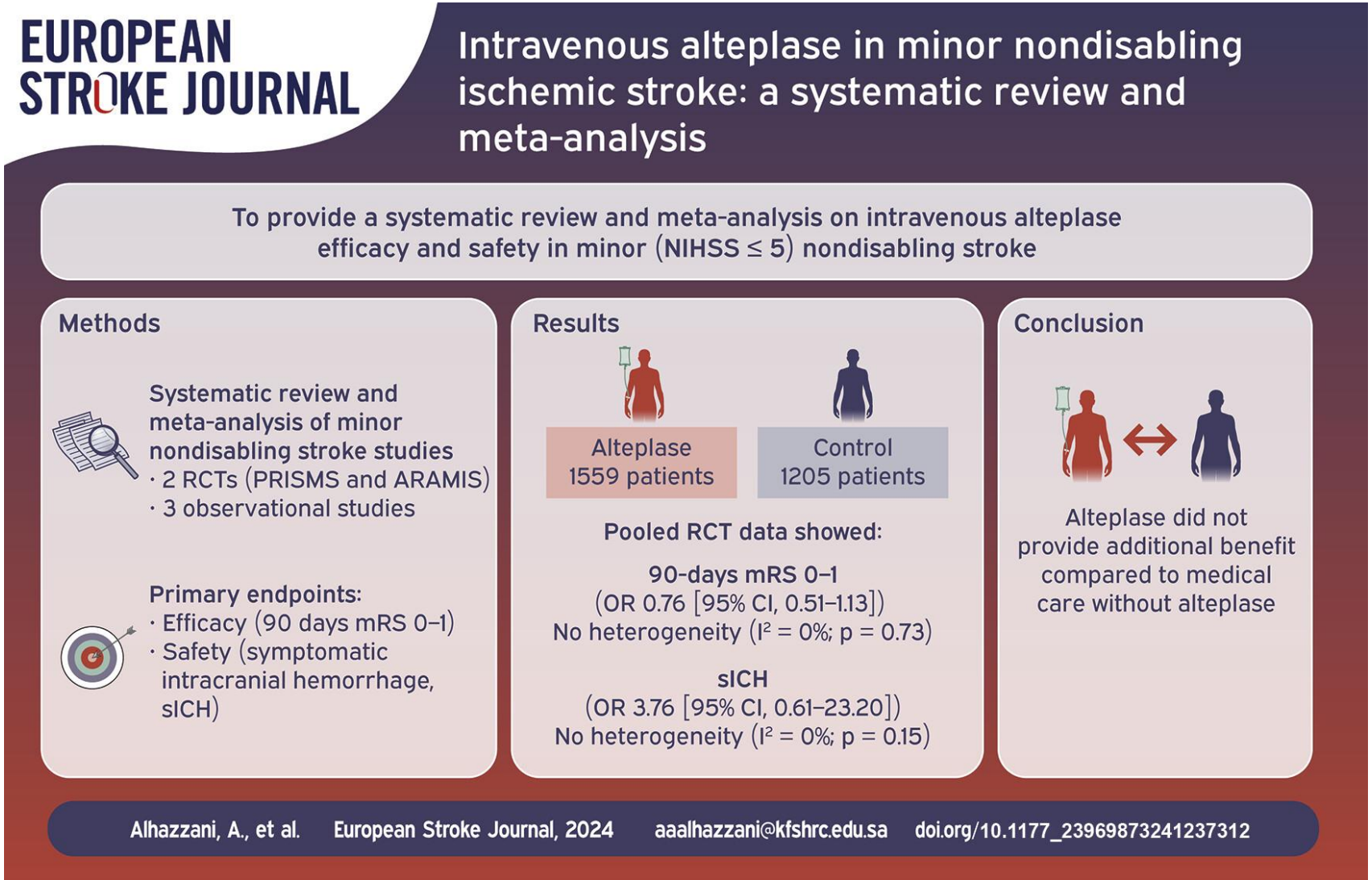
Conclusions

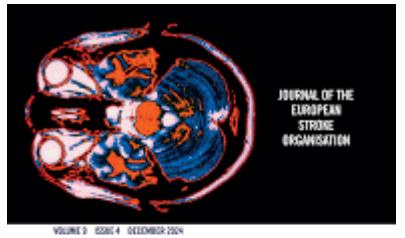
In our analysis, DAPT was associated with lower rates of symptomatic intracranial hemorrhage when compared to IV alteplase in patients with minor ischemic stroke. Additionally, no differences were found between 90-day outcomes of Modified Rankin Scale 0-1 or 0-2 and all-cause mortality.

Viana *et al.* (2024)

- DA y FiV presentan similar mRS a los 90 días en ictus minor.
- Similar mortalidad.
- Más hemorragias sintomáticas intracraneales en FiV.

RÉPLICAS A ESTE ESTUDIO





EUROPEAN STROKE JOURNAL

- Alteplasa no tiene un beneficio adicional en ictus minor no discapacitantes comparado con el MTM

RÉPLICAS A ESTE ESTUDIO

THE LANCET Neurology

ARTICLES · Volume 403, Issue 10444, P2597-2605, June 15, 2024 Download Full Issue

Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial

Prof Shelagh B Coutts, MD [a,b,c,e] · Sandeep Ankolekar, FRCP [g] · Ramana Appireddy, MD [h] · Juan F Arenillas, PhD [i,j] · Zarina Assis, MD [k,l] · Peter Bailey, MD [m] · et al. Show more

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- Ensayo parado por futilidad. 886 pacientes.
- Similar tasa de mejoría funcional (mRS 3 meses). Aumento de mortalidad significativo y de hemorragias intracraneales (casi significativo).
- No hay beneficio y sí un posible daño de usar tenecteplasa en pacientes con oclusión de gran vaso e ictus minor (NIHSS < 5).

MUCHAS GRACIAS