Sesión bibliográfica 16 de Septiembre

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- Metformina en el cáncer de mama
- AMPA en embarazadas de alto riesgo y utilidad en pacientes con HTA gestacional o crónica
- Tratamiento de la hipertensión leve durante el embarazo

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Incidence of ischemic stroke in patients with asymptomatic severe carotid stenosis without surgical intervention

Chang WR, et al. JAMA 2022; 327: 1974-82

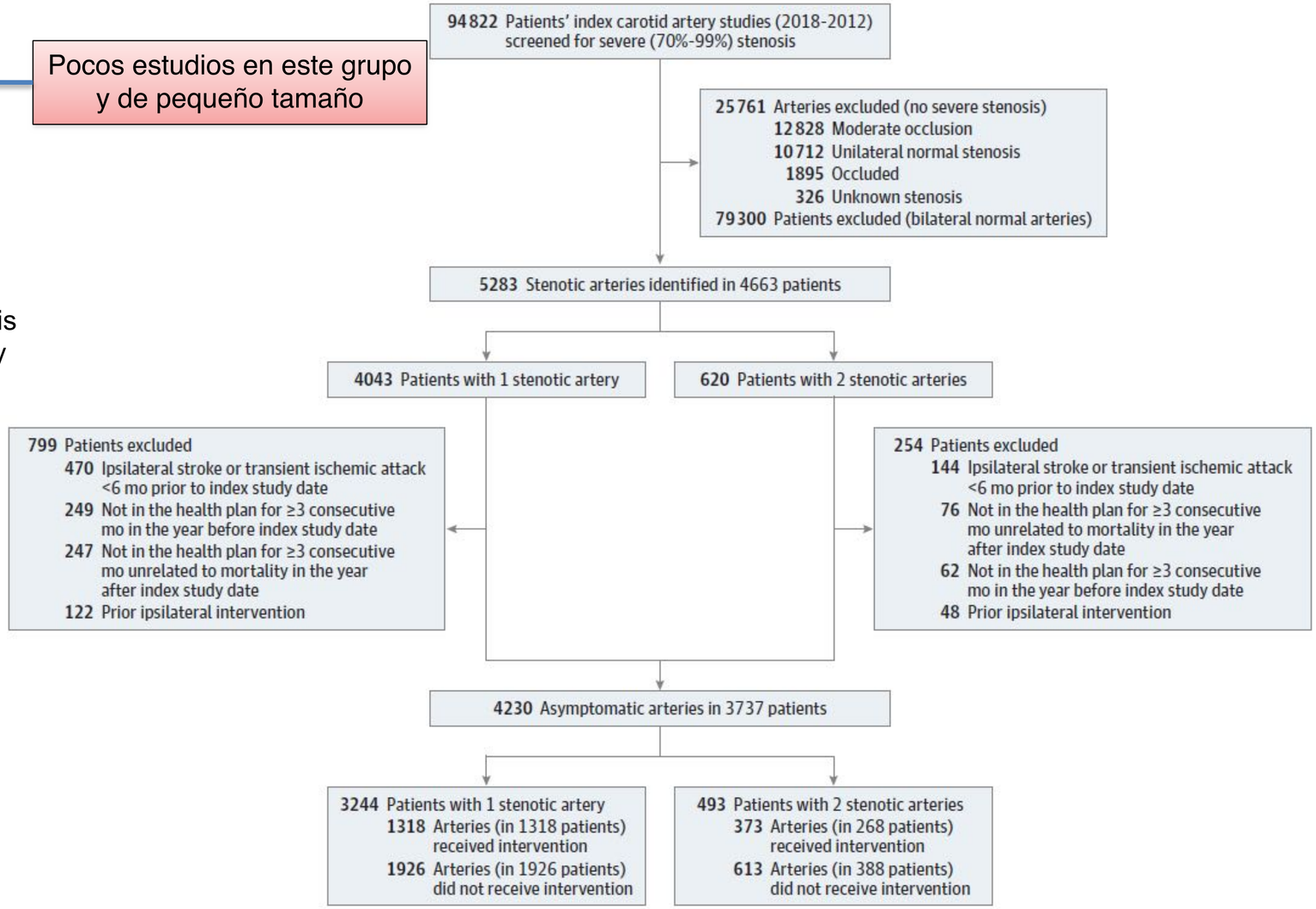
Estudios randomizados publicados entre 1995 y 2010 señalaban que el tratamiento óptimo era la cirugía en estos pacientes.
¿Cuál es el riesgo de ictus en los pacientes no intervenidos?

Pocos estudios en este grupo y de pequeño tamaño

ACST-1: 1123 pacientes con estenosis del 55-90% realizado entre 1992-1998 se observaba una incidencia de ictus del 10% a 5 años en pacientes no intervenidos

PACIENTES Y MÉTODOS

Estudio de cohortes retrospectivo con 3737 pacientes con estenosis carotídea (70-99%) asintomática diagnosticadas entre 2008-2012 y seguidos hasta 2019. Fuente: base de datos de 21 hospitales de California.
Excluyen pacientes con lesiones no arteroescleróticas (displasia, disección, etc), cirugía previa de carótida o ACV en los 6 meses previos.
Endpoint primario: ictus isquémico carotídeo secundario.



RESULTADOS

Edad media 73.8 años (DS 9.5), 58% varones y 73% de raza blanca.

Table 2. Stroke and All-Cause Mortality (per Unique Artery)

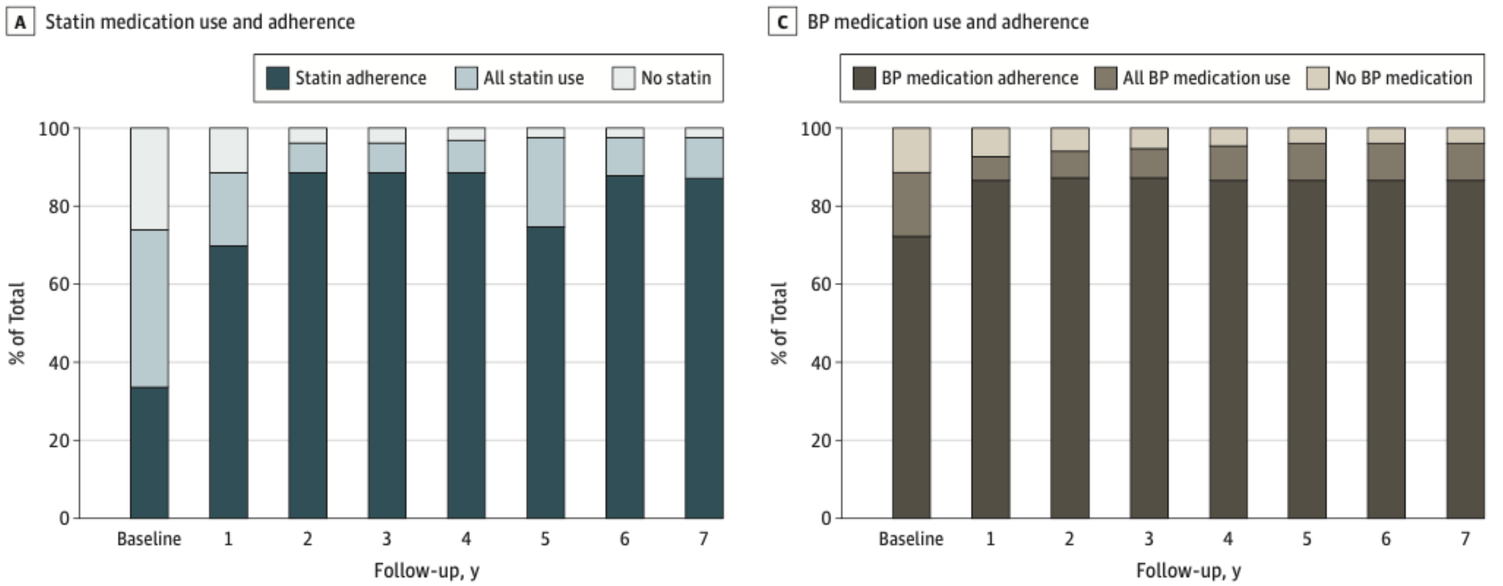
Endpoint primario

Outcomes	Cohort, % (95% CI) (N=4230)
Unadjusted overall crude rates, No. (%)	
Ipsilateral carotid-related stroke	133 (3.1)
All-cause mortality	2353 (55.6)
Mean yearly crude rates	
Ipsilateral carotid-related stroke	0.9 (0.7-1.2)
All-cause mortality	13.6 (12.6-14.7)
Kaplan-Meier unadjusted cumulative probabilities at 5 y	
Risk of ipsilateral carotid-related stroke	4.7 (3.9-5.7)
All-cause mortality	45.2 (43.4-46.9)
Unadjusted cumulative incidence of ipsilateral stroke (competing risk analysis), y	
1	1.0 (0.8-1.4)
2	1.6 (1.3-2.0)
3	2.1 (1.7-2.5)
4	2.5 (2.0-3.0)
5	2.7 (2.2-3.2)
6	2.8 (2.3-3.4)
7	2.9 (2.5-3.5)
8	3.2 (2.7-3.8)

TA media 130/68. Cifras de cLDL media de 87 mg/dl y persistencia de tabaquismo activo del 13%

Datos sobre adherencia al tratamiento médico

Figure 3. Per-Patient Medication Use, Adherence, and Effect Over Time



LIMITACIONES DEL ESTUDIO

Estudio retrospectivo de cohortes y posibilidad de sesgos
No se evalúa el uso de AAS
Dificultad para recoger todos los AIT previos (codificación)

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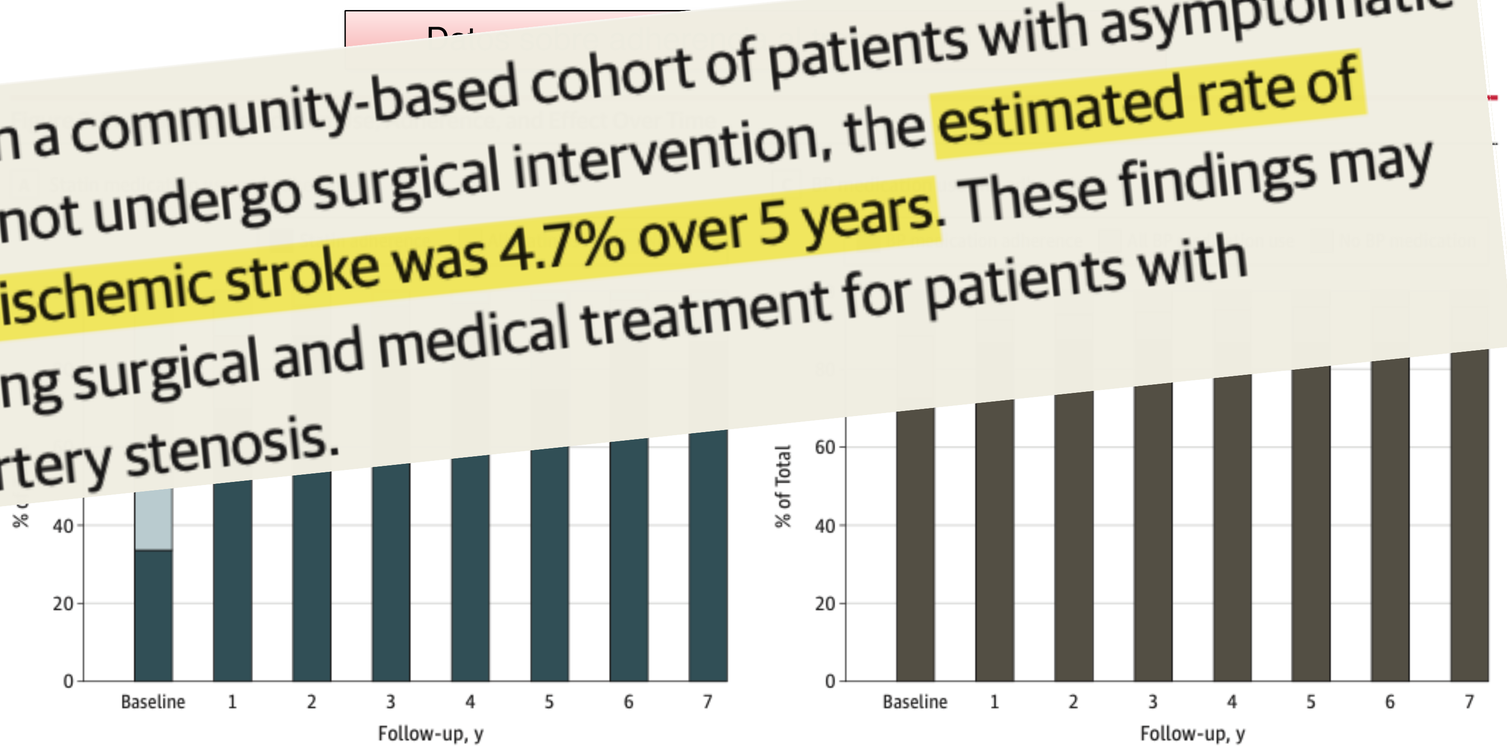
CONCLUSIONS AND RELEVANCE In a community-based cohort of patients with asymptomatic severe carotid stenosis who did not undergo surgical intervention, the estimated rate of ipsilateral carotid-related acute ischemic stroke was 4.7% over 5 years. These findings may inform decision-making regarding surgical and medical treatment for patients with asymptomatic severe carotid artery stenosis.



LIMITACIONES DEL ESTUDIO

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Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease

Joseph P, et al. Lancet 2021; 398: 1133-46

Mortalidad: 19 millones/año. Y otros 38 millones/año IAM no fatal.
Polypill → concepto introducido en el 2000
Mejoría de la adherencia y del control de factores de riesgo CV.

Cuestiones por resolver:

- ¿Debería el AAS formar parte de la polypill?
- Magnitud del beneficio en eventos CV específicos
- Seguridad
- ¿Diferencias en subgrupos específicos?

PACIENTES Y MÉTODOS

Metaanálisis de 3 ensayos clínicos (con más de 1000 pacientes y al menos 2 años de seguimiento).
Incluían polypill con y sin AAS.
Endpoint primario: compuesto de mortalidad cardiovascular, IAM, ictus o revascularización.

	TIPS-3	HOPE-3	PolyIran
Locations	Bangladesh, Canada, Colombia, India, Indonesia, Malaysia, Philippines, Tanzania, Tunisia	Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, South Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, UK, Ukraine	Iran
Overall trial population	5713 participants without known vascular disease but at intermediate cardiovascular disease risk*	12 705 participants without known vascular disease but at intermediate cardiovascular disease risk*	6838 participants with or without vascular disease
Population included in meta-analysis	All participants (n=5713)	Participants randomly assigned to double active group or double placebo group (polypill concept; n=6348)	Participants without a history of vascular disease (n=6101)
Study design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Pragmatic, cluster-randomised
Intervention†	2×2×2 factorial design: daily oral polypill consisting of simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg; daily aspirin 75 mg; monthly oral vitamin D 60 000 IU	2×2 factorial design: daily oral rosuvastatin 10 mg; daily oral candesartan 16 mg and hydrochlorothiazide 12·5 mg	Daily oral polypill consisting of atorvastatin 20 mg, hydrochlorothiazide 12·5 mg, enalapril 5 mg (or valsartan 40 mg), and aspirin 81 mg
Comparator (or control)†	Matching placebos	Matching placebos	Minimal care (blood pressure measurement and risk factor counselling)
Median (IQR) follow-up, years	4·4 (3·2–5·9)	5·5 (5·1–6·2)	5·0 (4·9–5·0)

*Based on estimated cardiovascular risk by the Framingham Risk Score. †Counselling to enhance healthy behaviours (eg, diet, activity, and avoidance of tobacco) was recommended for all participants in TIPS-3 and HOPE-3, and was included in both the intervention and control group in the PolyIran study.

Table 1: **Characteristics of included trials**

Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease

Joseph P, et al. Lancet 2021; 398: 1133-46

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Mejoría de la adherencia y del control de factores de riesgo CV.

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PACIENTES Y MÉTODOS

Metaanálisis de 3 ensayos clínicos (con más de 1000 pacientes y al menos 2 años de seguimiento).
Incluían polypill con y sin AAS.
Endpoint primario: compuesto de mortalidad cardiovascular, IAM, ictus o revascularización.

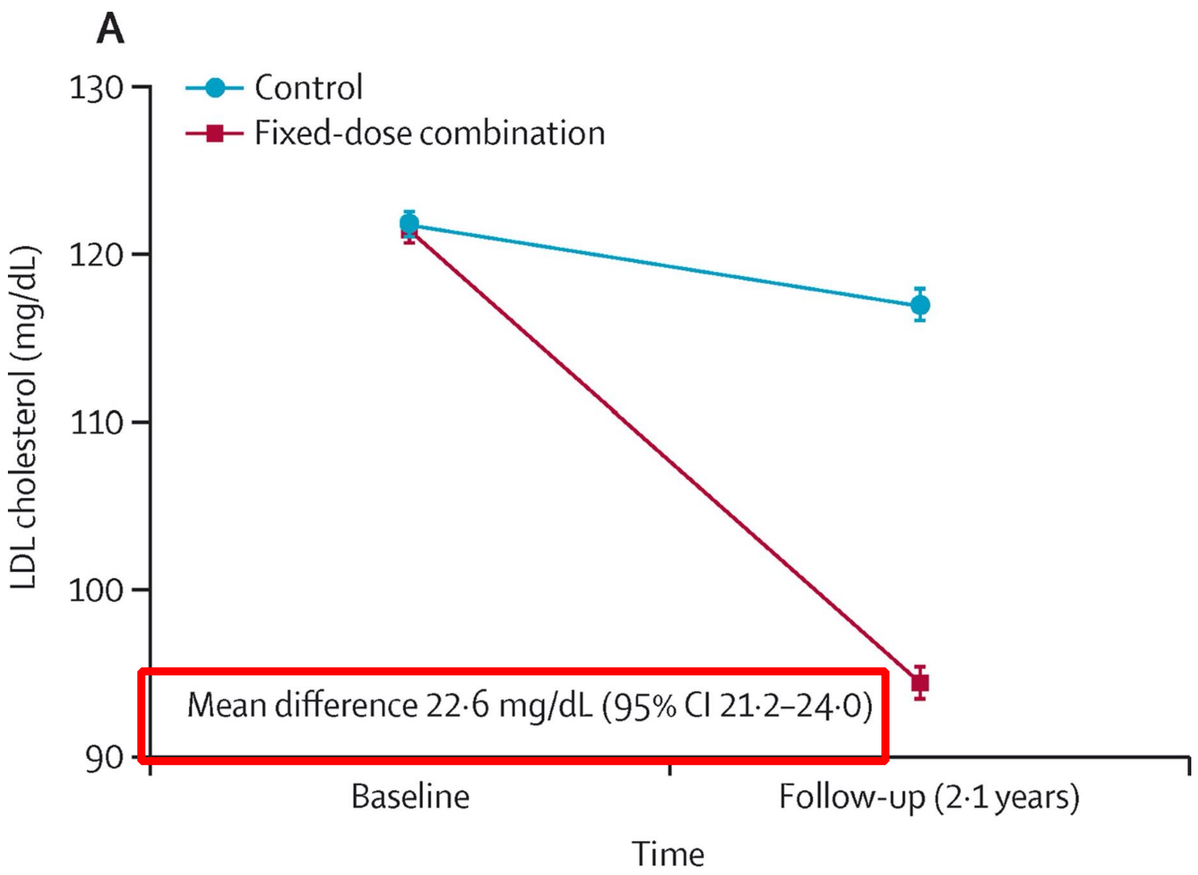
TIPS-3
Simvastatina 40 mg+Atenolol 100 mg+HTC 25 mg+Ramipril 10 mg vs control

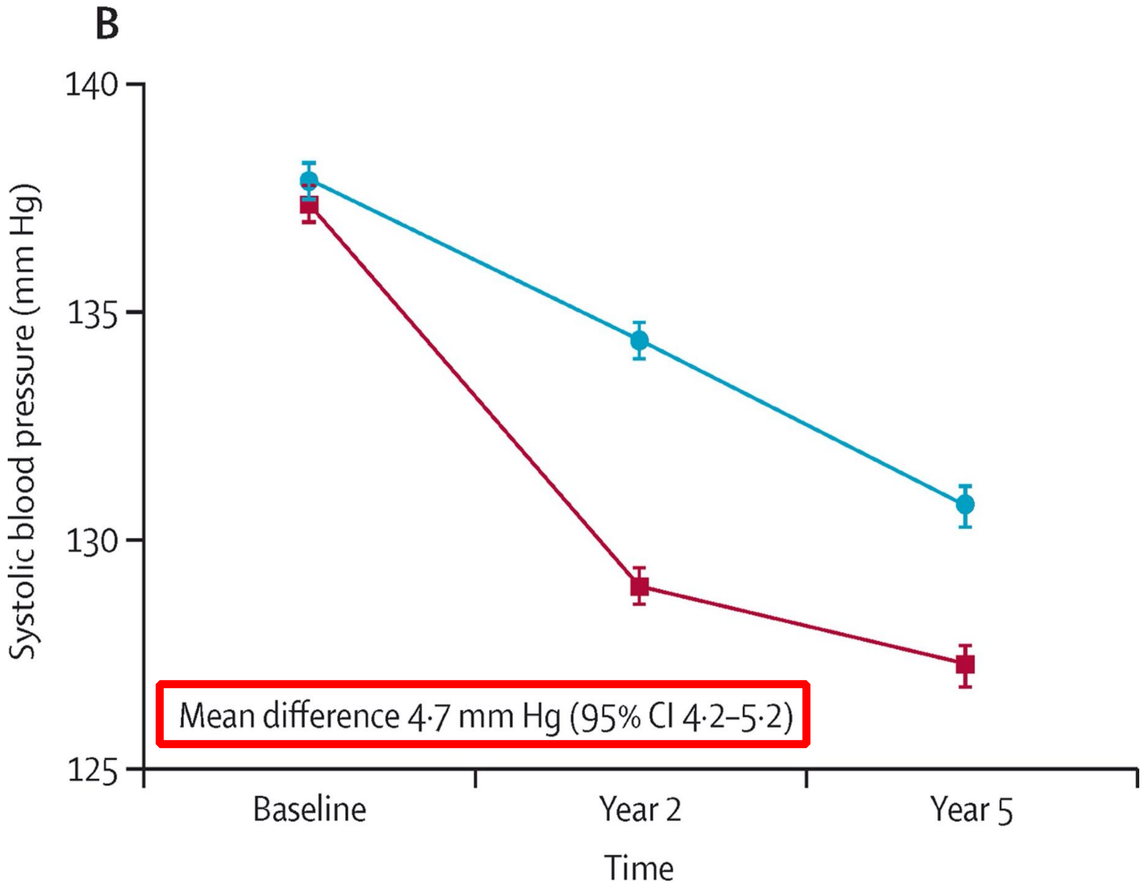
HOPE-3
Candesartan 16 mg+HTC 12.5 mg +Rosuvastatina 10 mg vs placebo

POLYIRAN:
Enalapril 5 mg+Atorvastatina 20 mg+HTC 12.5 mg

	Overall (n=18 162)	TIPS-3 (n=5713)	HOPE-3 (n=6348)	PolyIran (n=6101)
Age, years	63·0 (7·1)	63·9 (6·6)	65·7 (6·3)	59·3 (6·7)
Sex				
Female	9038 (49·8%)	3025 (52·9%)	2943 (46·4%)	3070 (50·3%)
Male	9124 (50·2%)	2688 (47·1%)	3405 (53·6%)	3031 (49·7%)
Diabetes	3523 (19·4%)	2095 (36·7%)	574 (9·0%)	854 (14·0%)
Hypertension	11 519 (63·4%)	4790 (83·8%)	3831 (60·3%)	2898 (47·5%)
Smoking history	4243 (23·4%)	1426 (25·0%)	1780 (28·0%)	1037 (17·0%)
Body-mass index, kg/m²	26·5 (5·0)	25·8 (4·7)	27·1 (4·7)	26·5 (5·3)
Blood pressure, mm Hg				
Systolic	137·7 (19·1)	144·5 (16·8)	138·1 (14·7)	130·8 (22·4)
Diastolic	81·5 (10·7)	83·9 (9·7)	81·9 (9·3)	78·7 (12·2)
Cholesterol, mg/dL				
Total	200·0 (43·3)	196·2 (45·6)	201·2 (42·6)	202·5 (41·4)
LDL	121·7 (37·4)	120·7 (40·7)	127·4 (36·5)	117·1 (34·1)
HDL	50·6 (14·9)	47·7 (13·0)	44·7 (14·0)	58·9 (13·7)
Cholesterol, mmol/L				
Total	5·2 (1·1)	5·1 (1·2)	5·2 (1·1)	5·2 (1·1)
LDL	3·1 (1·0)	3·1 (1·1)	3·3 (0·9)	3·0 (0·9)
HDL	1·3 (0·4)	1·2 (0·3)	1·2 (0·4)	1·5 (0·4)
Fasting plasma glucose, mg/dL	105·7 (37·7)	114·3 (45·0)	99·1 (21·9)	104·6 (41·3)
Fasting plasma glucose, mmol/L	5·9 (2·1)	6·3 (2·5)	5·5 (1·2)	5·8 (2·3)
Creatinine, mg/dL	1·0 (0·2)	0·9 (0·3)	0·9 (0·2)	1·1 (0·2)
Creatinine, mmol/L	84·5 (22·0)	81·5 (23·3)	79·3 (19·0)	92·8 (21·2)
10-year estimated cardiovascular disease risk, %	17·7% (8·7)	19·9% (8·1)	19·9% (7·9)	13·5% (8·6)

RESULTADOS





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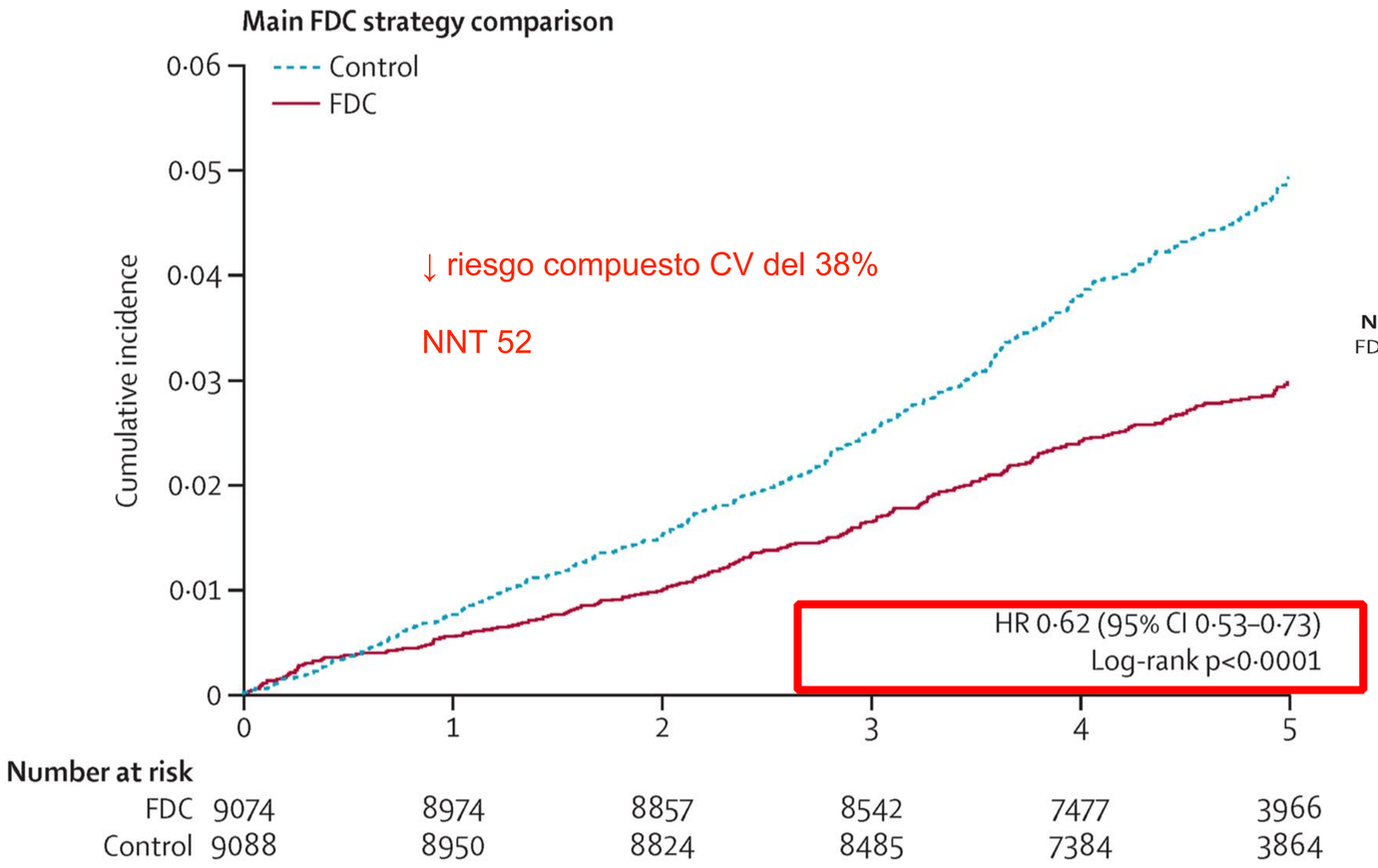
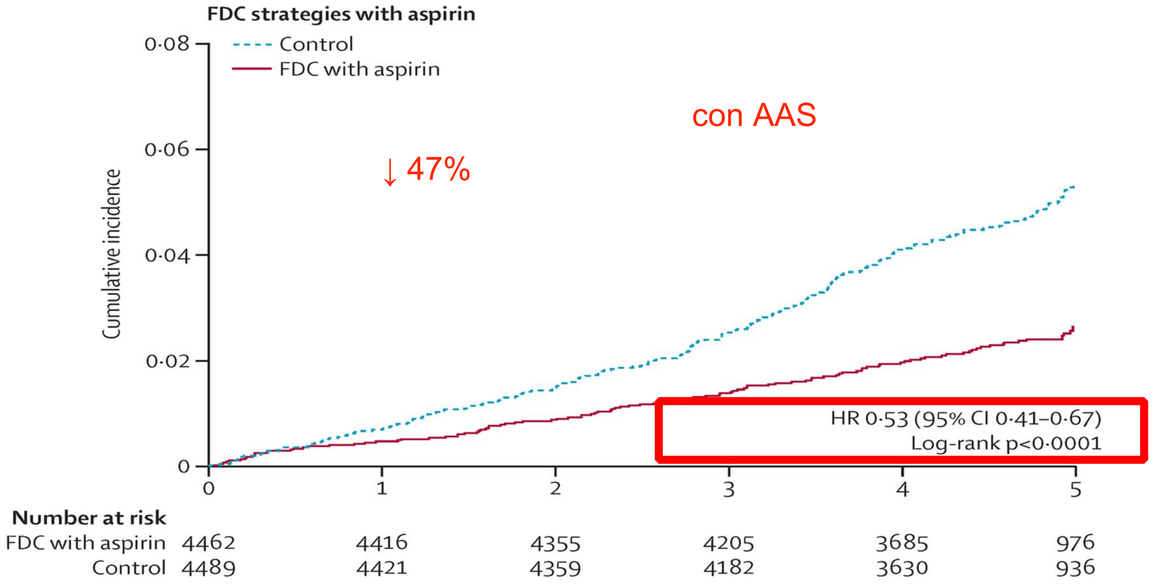
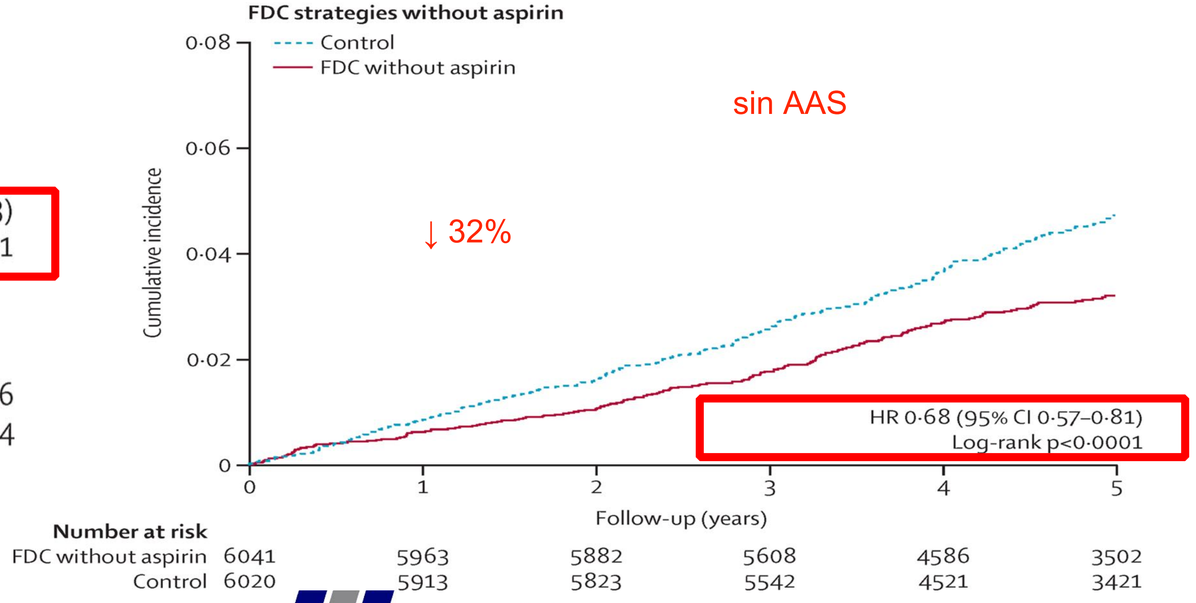
RESULTADOS

Endpoint primario







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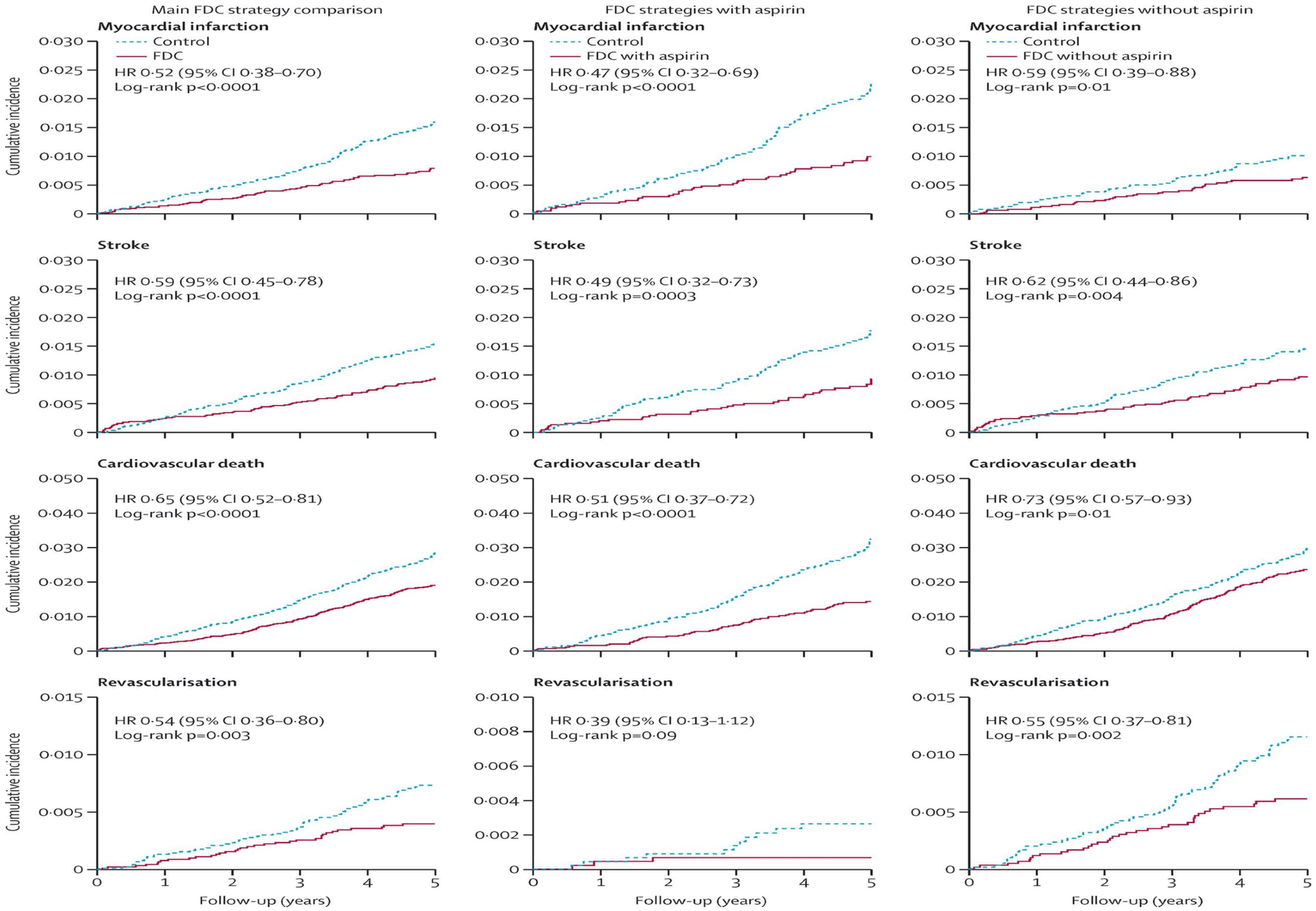
Joseph P, et al. Lancet 2021; 398: 1133-46

RESULTADOS



Similares resultados desglosando el compuesto en los polypill con/sin AAS

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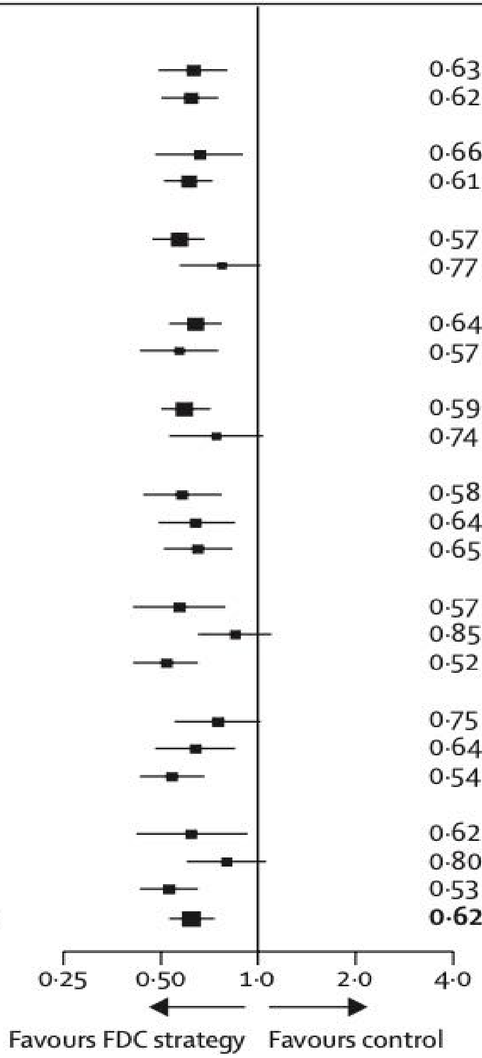
RESULTADOS

A	Events/participants (%)		HR (95% CI)	p value for interaction or trend*
	FDC strategy	Control		
Sex				
Female	109/4553 (2·4%)	171/4485 (3·8%)	0·63 (0·49–0·80)	
Male	167/4521 (3·7%)	274/4603 (6·0%)	0·62 (0·50–0·75)	0·82
Hypertension				
No	69/3326 (2·1%)	105/3317 (3·2%)	0·66 (0·48–0·90)	
Yes	207/5748 (3·6%)	340/5771 (5·9%)	0·61 (0·51–0·72)	0·58
Diabetes				
No	189/7306 (2·6%)	333/7333 (4·5%)	0·57 (0·47–0·68)	
Yes	87/1768 (4·9%)	112/1755 (6·4%)	0·77 (0·57–1·02)	0·09
Smoking status				
Never smoked	197/6948 (2·8%)	308/6971 (4·4%)	0·64 (0·53–0·77)	
Ever smoked	79/2126 (3·7%)	137/2117 (6·5%)	0·57 (0·43–0·75)	0·46
BMI, kg/m²				
<30	211/7128 (3·0%)	359/7223 (5·0%)	0·59 (0·50–0·71)	
≥30	63/1933 (3·3%)	84/1858 (4·5%)	0·74 (0·53–1·04)	0·32
LDL cholesterol, mg/dL				
≤105	80/2994 (2·7%)	139/2942 (4·7%)	0·58 (0·44–0·77)	
>105 to 135	85/2838 (3·0%)	129/2805 (4·6%)	0·64 (0·49–0·85)	
>135	105/2869 (3·7%)	165/2963 (5·6%)	0·65 (0·51–0·83)	0·51
Systolic blood pressure, mm Hg				
≤130	65/3318 (2·0%)	113/3237 (3·5%)	0·57 (0·41–0·79)	
>130 to 144	100/2830 (3·5%)	121/2904 (4·2%)	0·85 (0·65–1·10)	
>144	111/2926 (3·8%)	211/2945 (7·2%)	0·52 (0·41–0·65)	0·35
Age, years				
≤60	78/3409 (2·3%)	106/3444 (3·1%)	0·75 (0·55–1·02)	
>60 to 66	82/2916 (2·8%)	125/2830 (4·4%)	0·64 (0·48–0·85)	
>66	116/2749 (4·2%)	214/2814 (7·6%)	0·54 (0·43–0·68)	0·06
Estimated 10-year CVD risk				
≤12%	43/2984 (1·4%)	67/2829 (2·4%)	0·62 (0·42–0·93)	
>12% to 22%	84/2914 (2·9%)	109/3032 (3·6%)	0·80 (0·60–1·06)	
>22%	135/3056 (4·4%)	258/3126 (8·3%)	0·53 (0·43–0·65)	0·11
Overall	**276/9074 (3·0%)**	**445/9088 (4·9%)**	**0·62 (0·53–0·73)**	



Beneficio en todos los subgrupos

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RESULTADOS

Ahora en porcentajes…

	Control	Fixed-dose combination	HR (95% CI)	p value
Fixed-dose combination strategy versus control				
Randomised participants	9088	9074	..	..
Primary outcome	445 (4·9%)	276 (3·0%)	0·62 (0·53–0·73)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, or angina	545 (6·0%)	362 (4·0%)	0·67 (0·58–0·77)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, angina, or heart failure	563 (6·2%)	377 (4·2%)	0·68 (0·59–0·78)	<0·0001
Individual cardiovascular outcomes				
Cardiovascular death*	227 (2·5%)	144 (1·6%)	0·65 (0·52–0·81)	<0·0001
Myocardial infarction	139 (1·5%)	70 (0·8%)	0·52 (0·38–0·70)	<0·0001
Stroke†	141 (1·6%)	83 (0·9%)	0·59 (0·45–0·78)	0·0002
Haemorrhagic stroke	27 (0·3%)	19 (0·2%)	0·69 (0·38–1·24)	..
Other stroke	115 (1·3%)	65 (0·7%)	0·57 (0·42–0·78)	..
Revascularisation	70 (0·8%)	39 (0·4%)	0·54 (0·36–0·80)	0·0023
Heart failure	39 (0·4%)	29 (0·3%)	0·75 (0·46–1·23)	0·25
Angina	141 (1·6%)	109 (1·2%)	0·80 (0·61–1·05)	0·10
Non-cardiovascular death*	299 (3·3%)	327 (3·6%)	1·08 (0·91–1·28)	0·36
All deaths*	526 (5·8%)	471 (5·2%)	0·90 (0·79–1·03)	0·13

Además la reducción del riesgo de eventos aumentaba con el tiempo

	Fixed-dose combination *vs* control	Fixed-dose combination with aspirin *vs* control	Fixed-dose combination without aspirin *vs* control
Randomisation to 1 year	0·73 (0·50–1·06)	0·68 (0·39–1·19)	0·74 (0·48–1·13)
1 year to 3 years	0·63 (0·48–0·81)	0·49 (0·33–0·72)	0·66 (0·48–0·89)
>3 years	0·58 (0·46–0·72)	0·51 (0·36–0·72)	0·68 (0·52–0·88)
Overall	0·62 (0·53–0·73)	0·53 (0·41–0·67)	0·68 (0·57–0·81)

Data are hazard ratios (95% CIs).

Table 4: **Effect of fixed-dose combination strategies on the primary outcome over time**

RESULTADOS

Ahora en porcentajes…

Además la reducción del riesgo de eventos aumentaba con el tiempo

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Randomisation to 1 year	0·73 (0·50–1·06)	0·68 (0·39–1·19)	[illegible]
1 year to 3 years	[illegible]	[illegible]	[illegible]
>3 years	[illegible]	[illegible]	[illegible]
Overall	[illegible]	[illegible]	[illegible]

Data are hazard rati[illegible]

Table 4: Effect of f[illegible]-dose combination strategies on the primary outcome over time

Interpretation Fixed-dose combination treatment strategies substantially reduce cardiovascular disease, myocardial infarction, stroke, revascularisation, and cardiovascular death in primary cardiovascular disease prevention. These benefits are consistent irrespective of cardiometabolic risk factors.

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Polypill strategy in secondary cardiovascular prevention

Castellano JM, et al. New Engl J Med 2022. DOI: 10.1056/NEJMoa2208275

¿Y en prevención secundaria?

PACIENTES Y MÉTODOS

Estudio randomizado.
Pacientes con IAM tipo 1 en los 6 meses previos.
Edad:
- Mayores de 75 años
- Mayores de 65 años con un factor de riesgo (DM, ERC, IAM o ictus previo).

Excluyen pacientes anticoagulados.

Polypill: AAS 100 mg, Ramipril (2.5 – 5 – 7.5 mg), Atorvastatina (20 – 40 mg)

Endpoint primario: compuesto mortalidad cardiovascular, IAM o ictus no fatal o revascularización urgente.

RESULTADOS

Grupos con características clínicas similares.
Abandono tratamiento 14% en ambos grupos.
Duración media del seguimiento: 2.3 años

Comorbilidades:
78% HTA
57% Diabetes
51% Tabaquismo
cLDL medio 89±37 mg/dl

Table 1. Demographic Characteristics of the Patients at Baseline.*

Characteristic	Polypill Group (N=1237)	Usual-Care Group (N=1229)
Age		
Mean — yr	75.8±6.7	76.1±6.5
Distribution — no. (%)		
<75 yr	516 (41.7)	482 (39.2)
≥75 yr	721 (58.3)	747 (60.8)
Sex — no. (%)		
Male	853 (69.0)	848 (69.0)
Female	384 (31.0)	381 (31.0)
Country — no. (%)		
Czech Republic	85 (6.9)	87 (7.1)
France	74 (6.0)	70 (5.7)
Germany	182 (14.7)	184 (15.0)
Hungary	45 (3.6)	45 (3.7)
Italy	366 (29.6)	365 (29.7)
Poland	63 (5.1)	60 (4.9)
Spain	422 (34.1)	418 (34.0)

Tratamiento grupo control: 40% estatinas, 98% IECAs y 95% AAS

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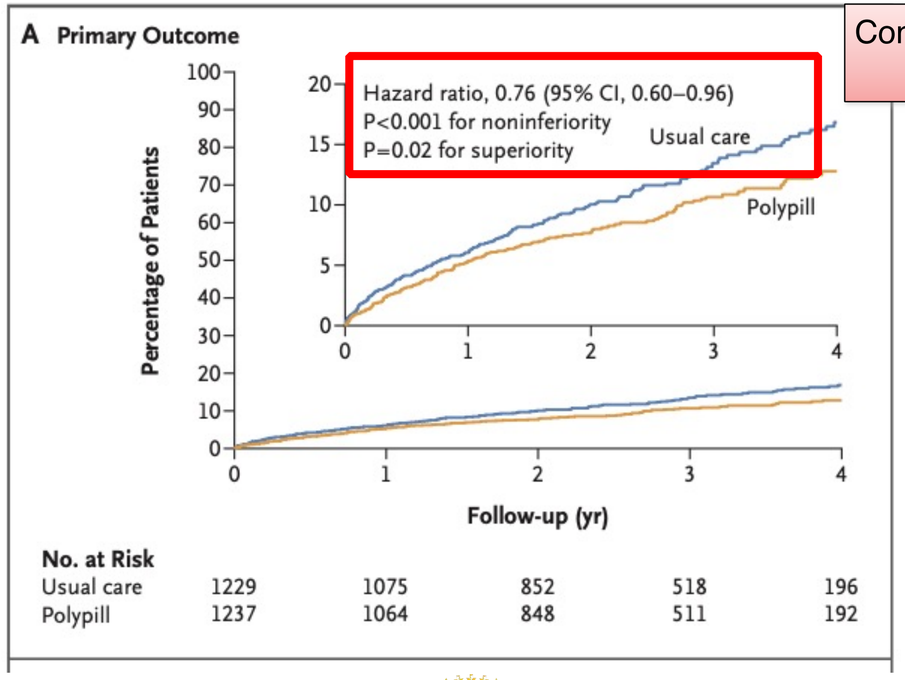
RESULTADOS

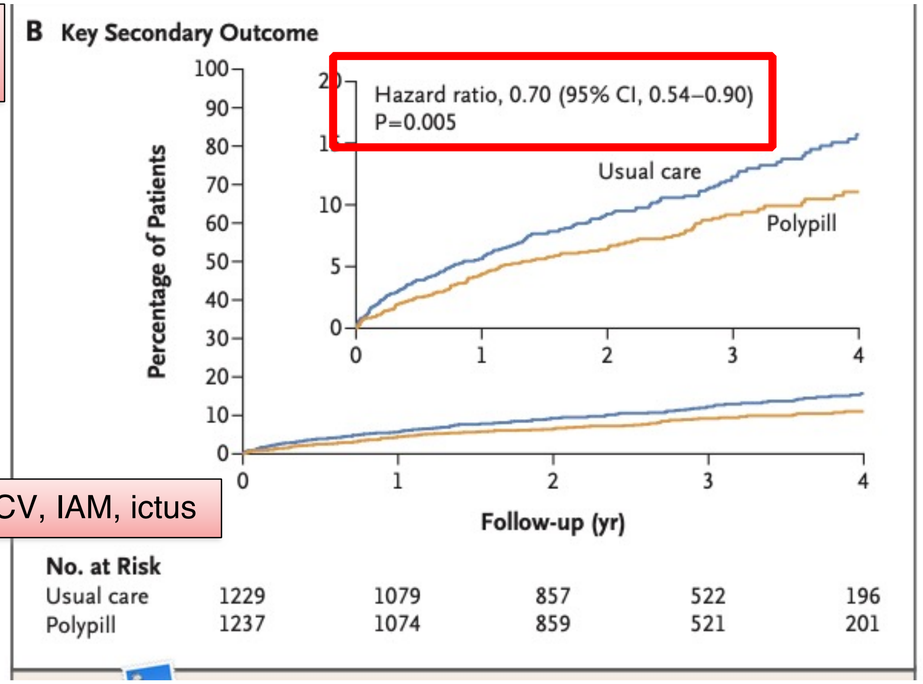
Table 2. Treatment Adherence at 6 Months and 24 Months.*

Treatment Adherence	Polypill Group				Usual-Care Group				Risk Ratio (95% CI)†
	No. of Patients	Low	Medium	High	No. of Patients	Low	Medium	High	
		number of patients (percent)				*number of patients (percent)*			
At 6 mo	1077	59 (5.5)	258 (24.0)	760 (70.6)	1057	100 (9.5)	294 (27.8)	663 (62.7)	1.13 (1.06–1.20)
At 24 mo	881	37 (4.2)	191 (21.7)	653 (74.1)	851	59 (6.9)	254 (29.8)	538 (63.2)	1.17 (1.10–1.25)

Mejoría de la adherencia



Compuesto mortalidad CV, IAM, ictus y revascularización



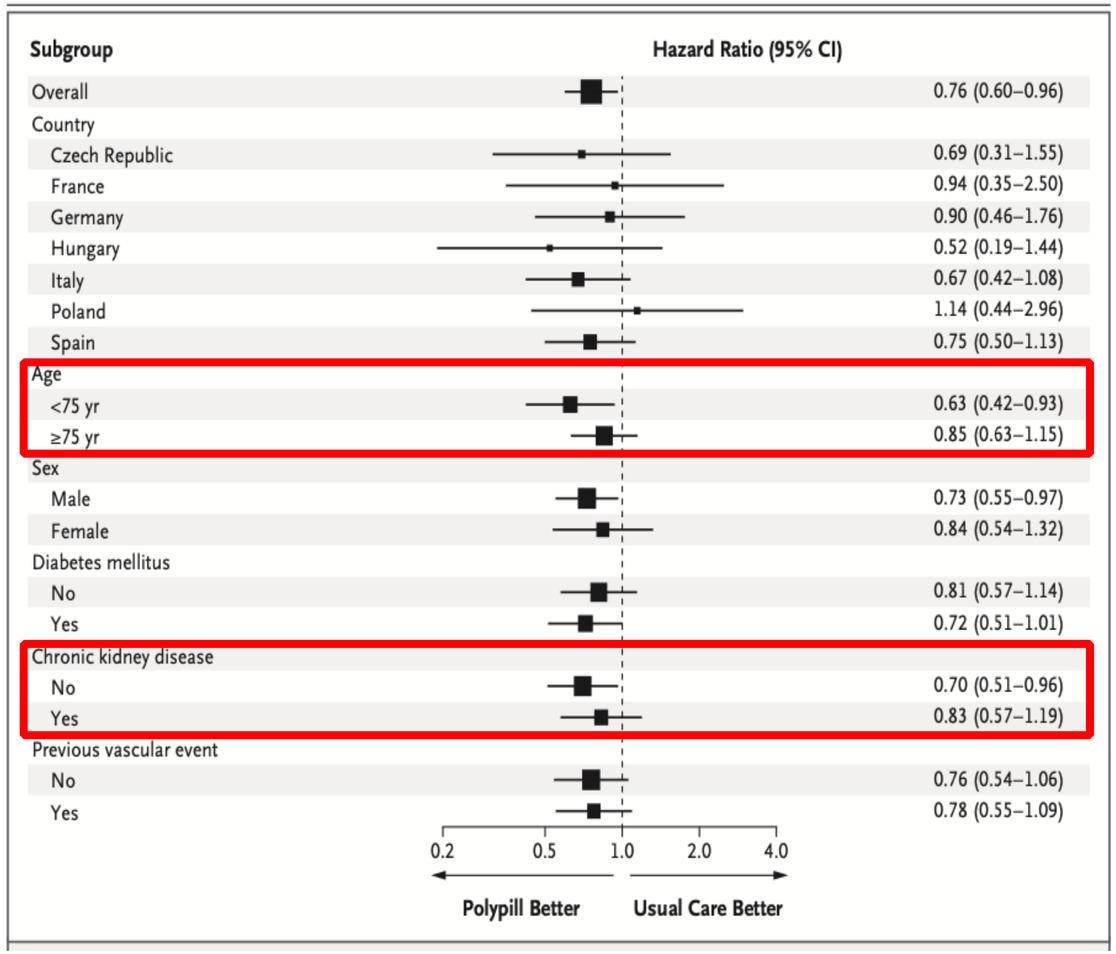
Compuesto mortalidad CV, IAM, ictus

RESULTADOS

Table 3. Primary and Secondary Outcomes.

Outcome	Polypill (N=1237)	Usual Care (N=1229)	Hazard Ratio (95% CI)*	P Value
	number of patients (percent)			
Primary outcome†	118 (9.5)	156 (12.7)	0.76 (0.60–0.96)	<0.001 for noninferiority; 0.02 for superiority
Key secondary outcome				
Composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke	101 (8.2)	144 (11.7)	0.70 (0.54–0.90)	0.005
Components of primary outcome				
Cardiovascular death	48 (3.9)	71 (5.8)	0.67 (0.47–0.97)	
Nonfatal type 1 myocardial infarction	44 (3.6)	62 (5.0)	0.71 (0.48–1.05)	
Nonfatal ischemic stroke	19 (1.5)	27 (2.2)	0.70 (0.39–1.26)	
Urgent revascularization	27 (2.2)	28 (2.3)	0.96 (0.57–1.63)	
Safety				
Death from any cause	115 (9.3)	117 (9.5)	0.97 (0.75–1.25)	
Death from noncardiovascular cause	67 (5.4)	46 (3.7)	1.42 (0.97–2.07)	

pNS



¿POR QUÉ ESTOS RESULTADOS?
Mayor adherencia
Efectos pleiotrópicos de estatinas e IECAs

LIMITACIONES: Estudio no ciego y efecto de la pandemia…

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RESULTADOS

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Nonfatal ischemic				
Urgent revascularizat				
Safety				
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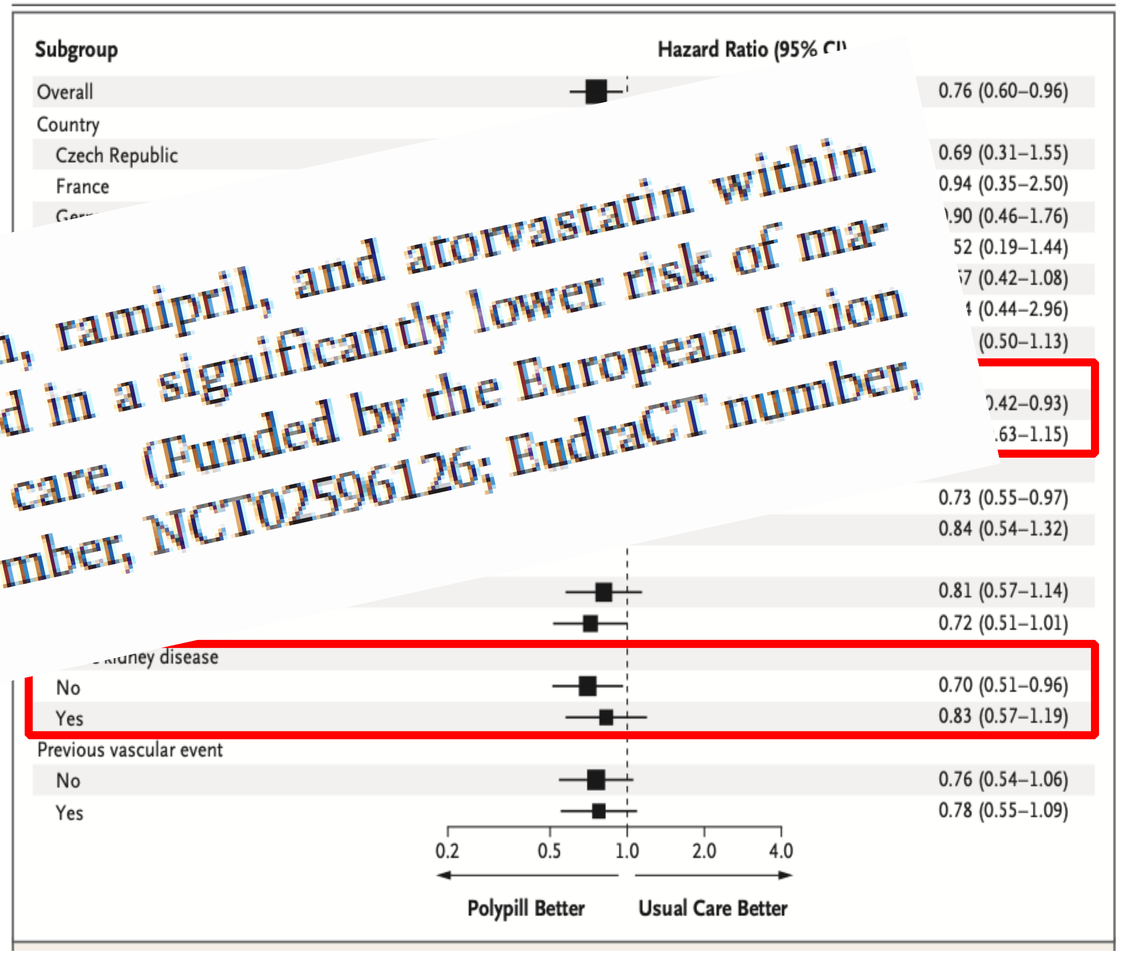
Death from noncardiovas		46 (3.7)	1.42 (0.97–2.07)	

CONCLUSIONS

Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care. (Funded by the European Union Horizon 2020; SECURE ClinicalTrials.gov number, NCT02596126; EudraCT number, 2015-002868-17.)



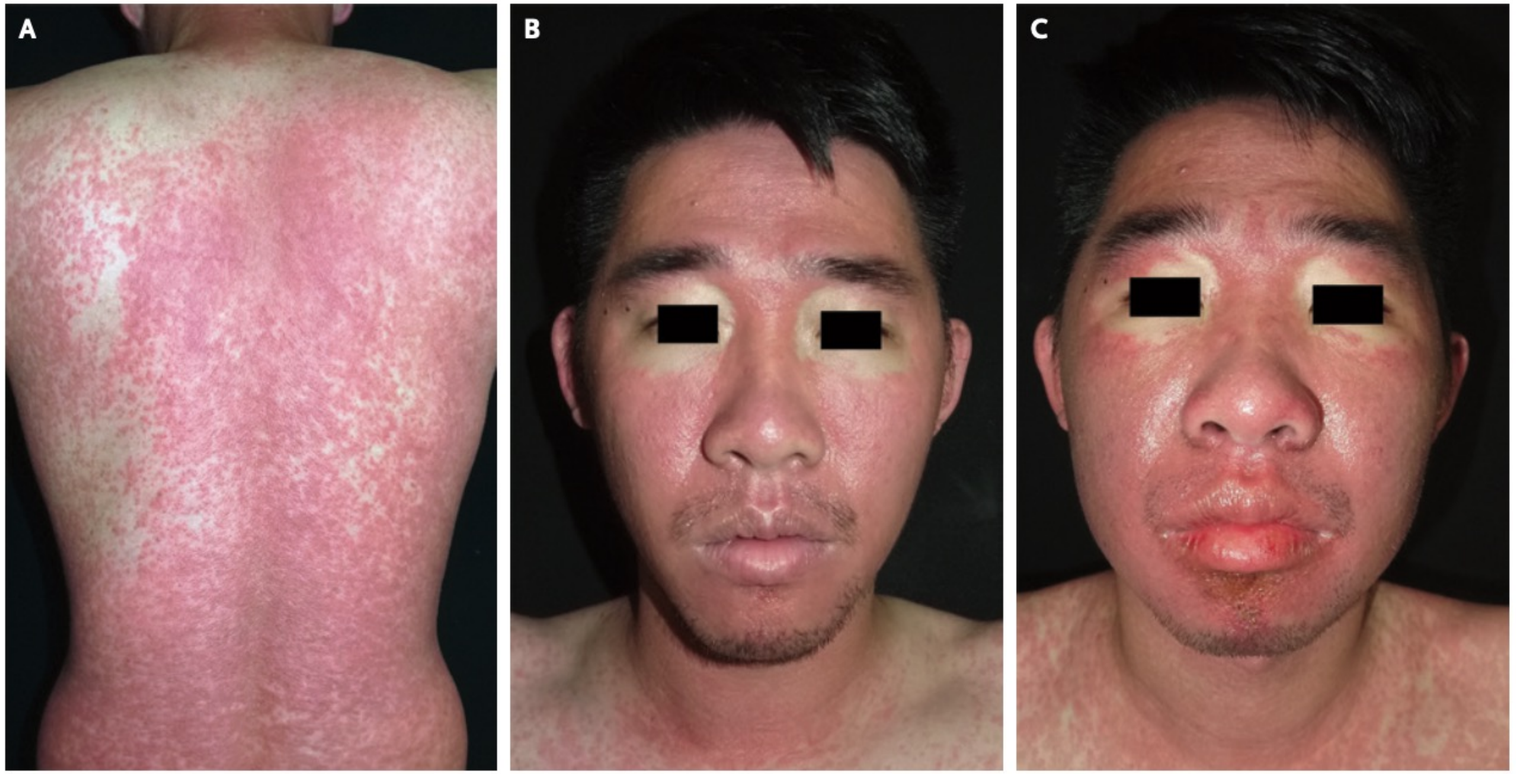
¿POR QUÉ ESTOS RESULTADOS?
Mayor adherencia
Efectos pleiotrópicos de estatinas e IECAs

LIMITACIONES: Estudio no ciego y efecto de la pandemia…

IMAGES IN CLINICAL MEDICINE

Stephanie V. Sherman, M.D., *Editor*

Drug Reaction with Eosinophilia and Systemic Symptoms



Varón de 30 años con fiebre y rash de 2 semanas de evolución.Llevaba 4 semanas en tratamiento con TMP/SMZ para una foliculitis.

A los 4 días de ingreso edema facial.
Analíticas: AST 989, ALT 162

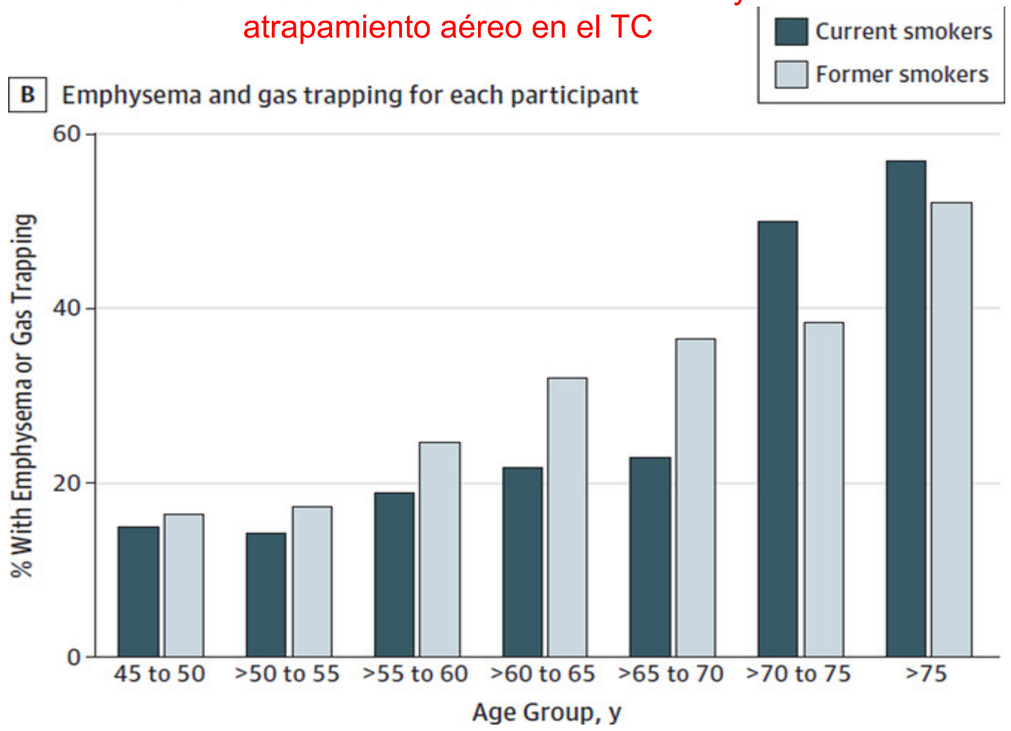
BX cutánea: dermatitis de interfase con infiltrado eosinofilico y linfocítico
Se trató con corticoides y ciclosporina

Bronchodilators in tobacco-exposed persons with symptons and preserved lung function

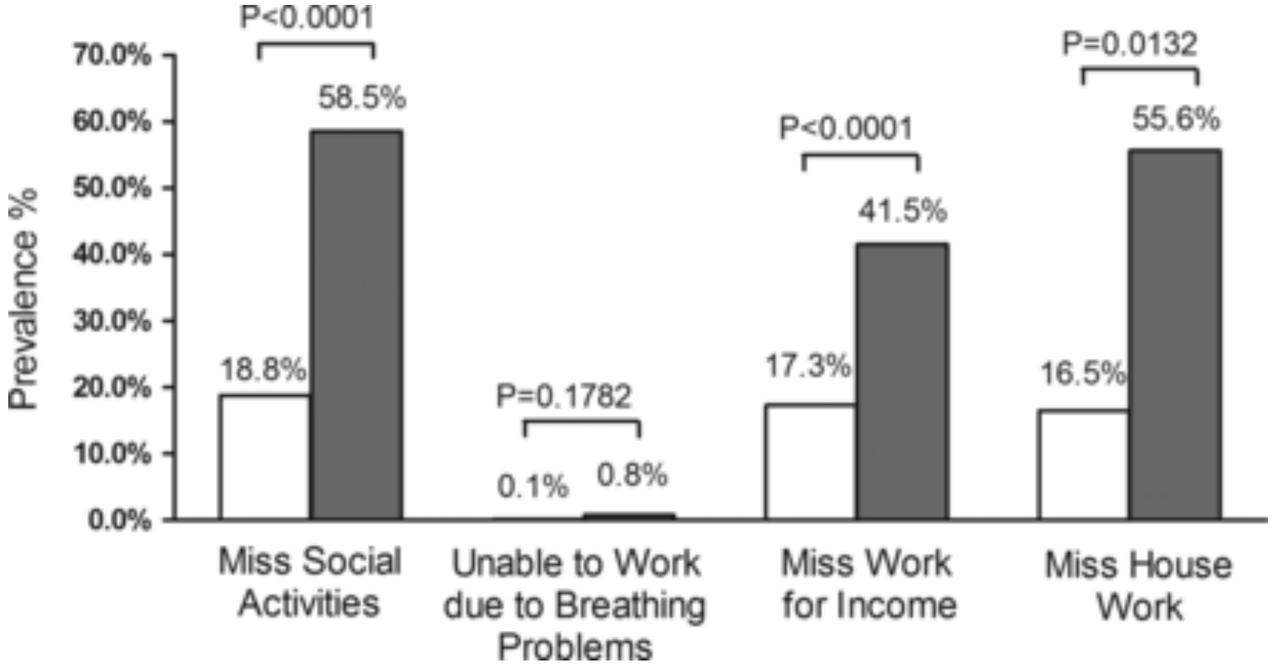
Han MK, et al. New Engl J Med 2022. DOI: 10.1056/NEJMoa2204752

Pre-EPOC: pacientes con antecedente de tabaquismo con síntomas respiratorios y exacerbaciones, pero con espirometría sin datos de obstrucción.
Puntuación CAT>10.

Cohorte COPDGene: datos de enfisema y atrapamiento aéreo en el TC



Cohorte CanCOLD: las exacerbaciones se relacionan con empeoramiento de la calidad de vida en estos pacientes



Hipótesis: ¿son útiles los broncodilatadores en estos pacientes?

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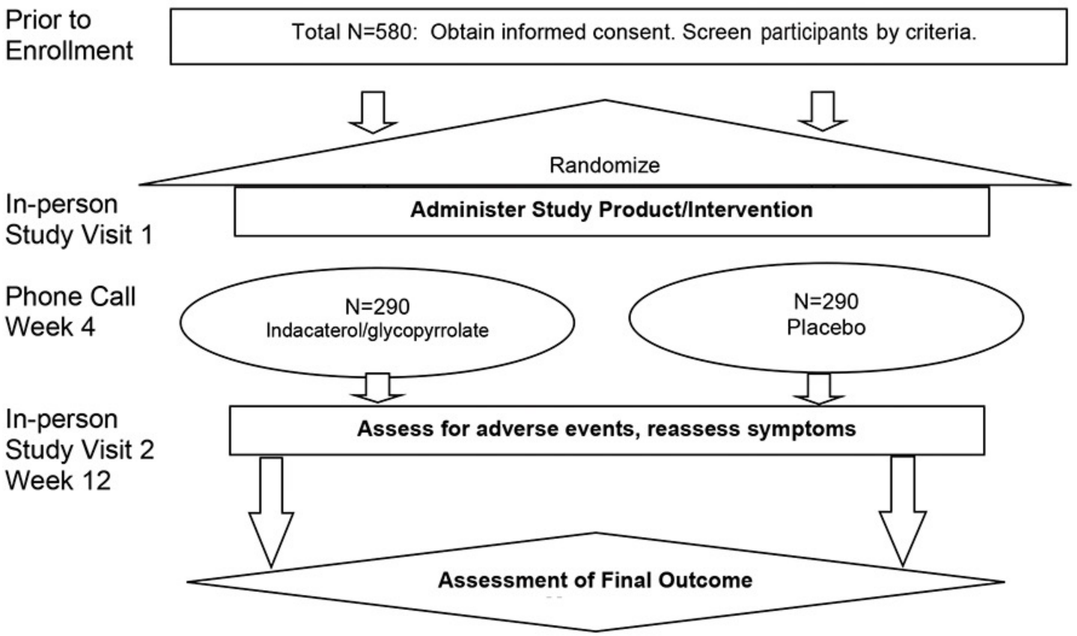
PACIENTES Y MÉTODOS

Pacientes entre 40-80 años con antecedente de tabaquismo (IPA>10) y puntuación en CAT>10
Espirometría: FEV1/FVC>0.70 y FCV>70% postbroncodilatador.

Criterios de exclusión:
- Asma bronquial
- Cualquier otra patología pulmonar concomitante
- Tratamiento previo con cualquier broncodilatador (y que no pudiesen realizar una retirada 30 días antes de su inclusión)

Randomización 1:1 → indacaterol + glicopirronio vs placebo durante 12 semanas
Espirometría basal y a las 12 semanas (fin de seguimiento)

Endpoint primario: mejoría de al menos 4 puntos en cuestionario SGRQ



PACIENTES Y MÉTODOS

Pacientes entre 40-80 años con antecedente de tabaquismo (IPA>10) y puntuación en CAT>10
Espirometría: FEV1/FVC<0.70 y FCV>70% postbroncodilatador.

Criterios de exclusión:
- Asma bronquial
- Cualquier otra patología pulmonar concomitante
- Tratamiento previo con cualquier broncodilatador (y que no pudiesen realizar una retirada 30 días antes de su inclusión)

Randomización 1:1 → indacaterol + glicopirronio vs placebo durante 12 semanas
Espirometría basal y a las 12 semanas (fin de seguimiento)

Endpoint primario: mejoría de al menos 4 puntos en cuestionario SGRQ.

RESULTADOS

Entre 2017 y 2021 reclutan 535 participantes en 20 centros (USA)

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Treatment (N=261)	Placebo (N=274)	Overall (N=535)
Age — yr	58.6±9.6	59.1±9.8	58.8±9.7
Male sex — no. (%)	127 (48.7)	133 (48.5)	260 (48.6)
Race — no. (%)†			
Black	92 (35.2)	99 (36.1)	191 (35.7)
White	148 (56.7)	154 (56.2)	302 (56.4)
Other	3 (1.1)	4 (1.5)	7 (1.3)
More than one race or missing race	18 (6.9)	17 (6.2)	35 (6.5)
Hispanic or Latino ethnic group — no. (%)†	25 (9.6)	22 (8.0)	47 (8.8)
Current smoking — no. (%)	169 (64.8)	174 (63.5)	343 (64.1)
Use of prohibited medication warranting washout — no. (%)‡	9 (3.4)	11 (4.0)	20 (3.7)
Body-mass index	29.5±4.9	29.4±5.3	29.5±5.1
Medical history — no./total no. (%)			
Coronary artery disease	12/252 (4.8)	11/264 (4.2)	23/516 (4.5)
Congestive heart failure	1/252 (0.4)	5/264 (1.9)	6/516 (1.2)
Chronic bronchitis§			
MRC definition	87/251 (34.7)	101/264 (38.3)	188/515 (36.5)
SGRQ definition	141/261 (54)	145/273 (53.1)	286/534 (53.6)
CAT definition	183/261 (70.1)	193/274 (70.4)	376/535 (70.3)
CAT score¶	17.5±6.7	17.6±6.0	17.6±6.4
SGRQ score‖	37.9±21.0	38.4±19.3	38.2±20.2
BDI score**	7.7±2.0	7.5±2.0	7.6±2.0
Postbronchodilator FEV_1 — % of predicted value	93.8±14.0	94.9±12.6	94.4±13.3
Postbronchodilator FVC — % of predicted value	92.9±12.8	94.2±13.3	93.6±13.0
Postbronchodilator FEV_1:FVC	0.78±0.05	0.78±0.05	0.78±0.05
Bronchodilator responsiveness — no. (%)††	30 (11.5)	32 (11.7)	62 (11.6)

PACIENTES Y MÉTODOS

Pacientes entre 40-80 años con antecedente de tabaquismo (IPA>10) y puntuación en CAT>10
Espirometría: FEV1/FVC>0.70 y FCV>70% postbroncodilatador.

Criterios de exclusión:
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- Cualquier otra patología pulmonar concomitante
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Espirometría basal y a las 12 semanas (fin de seguimiento)

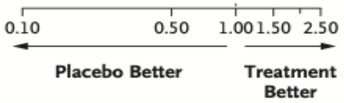
Endpoint primario: mejoría de al menos 4 puntos en cuestionario SGRQ.

RESULTADOS

Entre 2017 y 2021 reclutan 535 participantes en 20 centros (USA).
No hubo diferencias signifitcativas en el endpoint primario ni en los diferentes subgrupos

Tampoco hubo diferencias significativas en el FEV1 o en el CAT…

Outcome	Placebo (N=244)	Treatment (N=227)	Odds Ratio (95% CI)
	no. of participants/total no. (%)		
Primary outcome			
Overall			
Modified intention-to-treat analysis	144/244 (59.0)	128/227 (56.4)	0.91 (0.60–1.37)
Sensitivity analysis 1	143/242 (59.1)	129/230 (56.1)	0.89 (0.59–1.34)
Sensitivity analysis 2	144/240 (60.0)	124/220 (56.4)	0.87 (0.57–1.33)
Sensitivity analysis 3	115/196 (58.7)	109/192 (56.8)	0.98 (0.61–1.58)
Sensitivity analysis 4	146/249 (58.6)	131/232 (56.5)	0.93 (0.65–1.35)
Per-protocol analysis	110/176 (62.5)	101/170 (59.4)	0.88 (0.65–1.20)
Smoking status			
Current smoking	91/151 (60.3)	84/142 (59.2)	0.96 (0.54–1.70)
Former smoking	53/93 (57.0)	44/85 (51.8)	0.84 (0.47–1.52)
Body-mass index			
>30	63/108 (58.3)	47/93 (50.5)	0.80 (0.47–1.35)
≤30	81/136 (59.6)	81/134 (60.4)	1.00 (0.63–1.59)
Sex			
Female	68/125 (54.4)	61/115 (53.0)	0.88 (0.44–1.76)
Male	76/119 (63.9)	67/112 (59.8)	0.96 (0.72–1.28)
Age			
<65 yr	103/169 (60.9)	101/168 (60.1)	0.94 (0.60–1.46)
≥65 yr	41/75 (54.7)	27/59 (45.8)	0.72 (0.42–1.26)
Bronchodilator responsiveness			
Yes	16/25 (64.0)	14/27 (51.9)	0.66 (0.18–2.47)
No	128/219 (58.4)	114/200 (57.0)	0.96 (0.62–1.50)
Baseline inspiratory capacity			
<Median	72/122 (59.0)	68/116 (58.6)	1.02 (0.52–2.00)
≥Median	72/122 (59.0)	60/111 (54.1)	0.86 (0.55–1.36)
Baseline FEV_1 % of predicted			
<Median	66/112 (58.9)	61/109 (56.0)	0.93 (0.61–1.42)
≥Median	78/132 (59.1)	67/118 (56.8)	0.84 (0.46–1.55)
Presence of chronic bronchitis			
Yes	63/92 (68.5)	44/72 (61.1)	0.63 (0.27–1.49)
No	77/144 (53.5)	76/146 (52.1)	0.93 (0.56–1.55)
Secondary outcomes			
≥4-point improvement in SGRQ score plus TDI score of ≥1 without treatment failure	60/234 (25.6)	55/220 (25.0)	0.97 (0.60–1.57)
TDI score of ≥1 without treatment failure	80/234 (34.2)	80/220 (36.4)	1.14 (0.82–1.58)
≥2-point improvement in CAT score without treatment failure	166/244 (68.0)	169/227 (74.4)	1.45 (0.96–2.18)



DISCUSION

En “vida real” los médicos pautamos broncodilatadores en estos pacientes
La espirometría es infrautilizada en At. Primaria

Limitaciones:
- Síntomas pueden deberse a otras patologías respiratorias
- Efecto placebo en el grupo control o efecto Hawthorne (mejoría por estar incluido en u ensayo clínico)…
- Seguimiento de 12 semanas

CONCLUSIONS

Inhaled dual bronchodilator therapy did not decrease respiratory symptoms in symptomatic, tobacco-exposed persons with preserved lung function as assessed by spirometry. (Funded by the National Heart, Lung, and Blood Institute and others; RETHINC ClinicalTrials.gov number, NCT02867761.)

Outcome	Placebo (N=244)	Treatment (N=227)	Odds Ratio (95% CI)
	no. of participants/total no. (%)		
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Overall			
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Smoking status			
Current smoking	91/151 (60.3)	84/142 (59.2)	0.96 (0.54–1.70)
Former smoking	53/93 (57.0)	44/85 (51.8)	0.84 (0.47–1.52)
Body-mass index			
>30	63/108 (58.3)	47/93 (50.5)	0.80 (0.47–1.35)
≤30	81/136 (59.6)	81/134 (60.4)	1.00 (0.63–1.59)
Sex			
Female	68/125 (54.4)	61/115 (53.0)	0.88 (0.44–1.76)
Male	76/119 (63.9)	67/112 (59.8)	0.96 (0.72–1.28)
Age			
<65 yr	103/169 (60.9)	101/168 (60.1)	0.94 (0.60–1.46)
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≥Median	72/122 (59.0)	60/111 (54.1)	0.86 (0.55–1.36)
Baseline FEV_1 % of predicted			
<Median	66/112 (58.9)	61/109 (56.0)	0.93 (0.61–1.42)
≥Median	78/132 (59.1)	67/118 (56.8)	0.84 (0.46–1.55)
Presence of chronic bronchitis			
Yes	63/92 (68.5)	44/72 (61.1)	0.63 (0.27–1.49)
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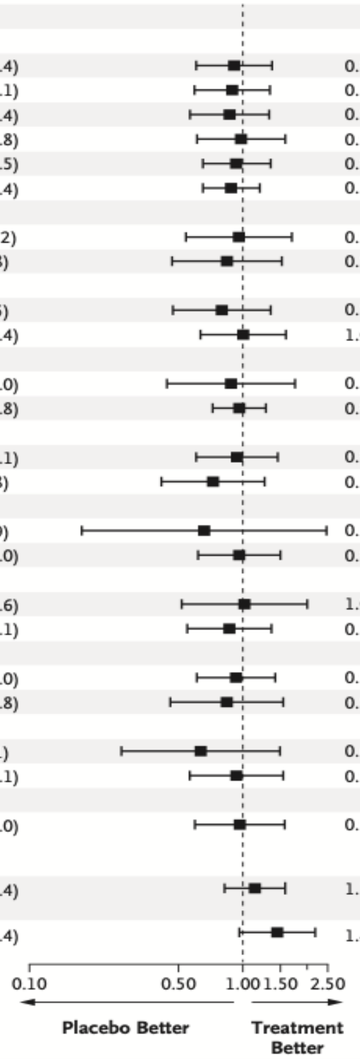


Effect of metformin vs placebo on invasive disease-free survival in patients with breast cancer

Goodwin PJ, et al. JAMA 2022; 327: 1963-73

Datos de estudios observacionales previos comentan posible efecto sobre la supervivencia

¿Mecanismo?
Reducción de las vías RAS y PI3K
Efecto antitumoral directo: activación de diferentes “kinasas” LKB1-y AKT

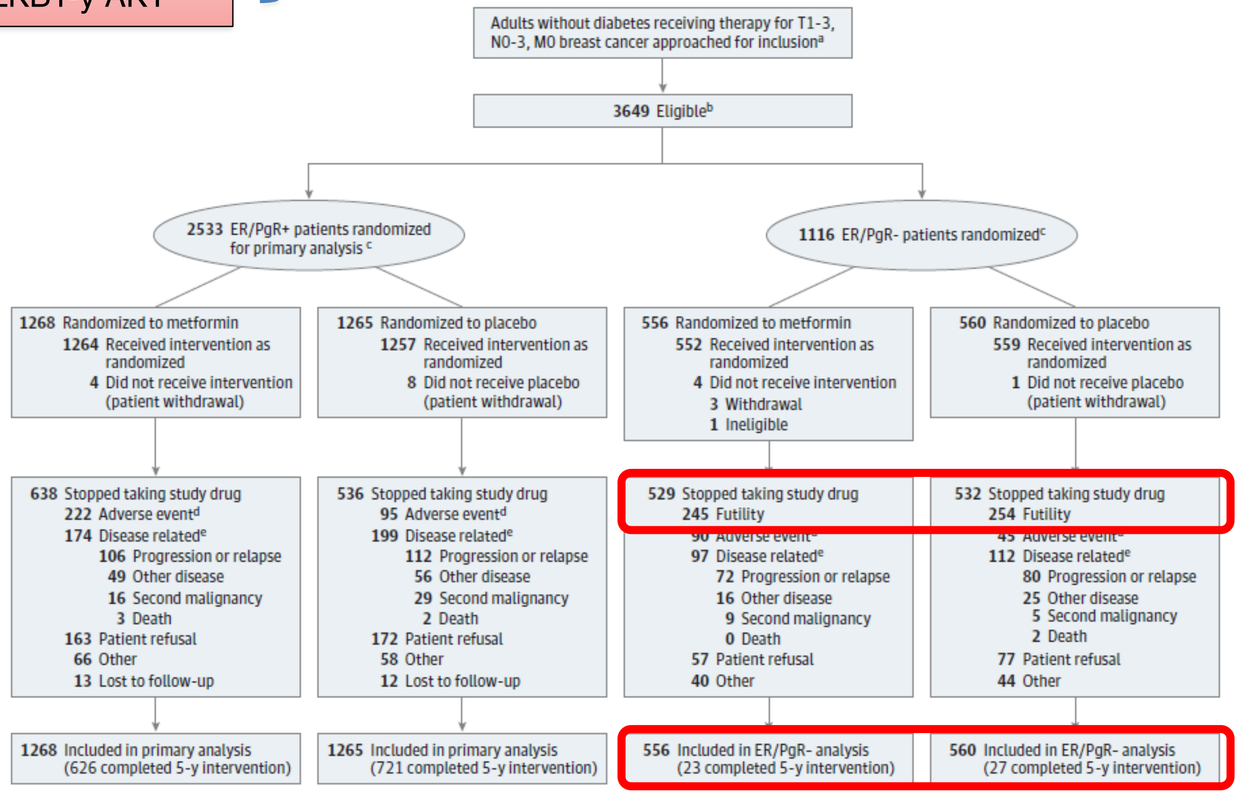
Dificultad de trasladar datos preclínicos a la práctica habitual
Uso in vitro de dosis elevadas de glucosa, insulina y metformina

Estudios randomizados con metformina en pacientes con cáncer de mama
reducción intratumoral de KI67 en subgrupo HER2+ (pero no en todos los trabajos)

PACIENTES Y MÉTODOS

Estudio de fase 3, randomizado vs placebo y doble ciego.
N= 3649 pacientes NO diabéticas con neoplasia de mama no metastásica (T1-T3) recogidas entre 2010 y 2013 con seguimiento hasta Oct/20.
Randomización 1:1 → Metformina 1700 mg/d vs placebo durante 5 años.

Endpoint primario: tiempo libre de enfermedad/supervivencia



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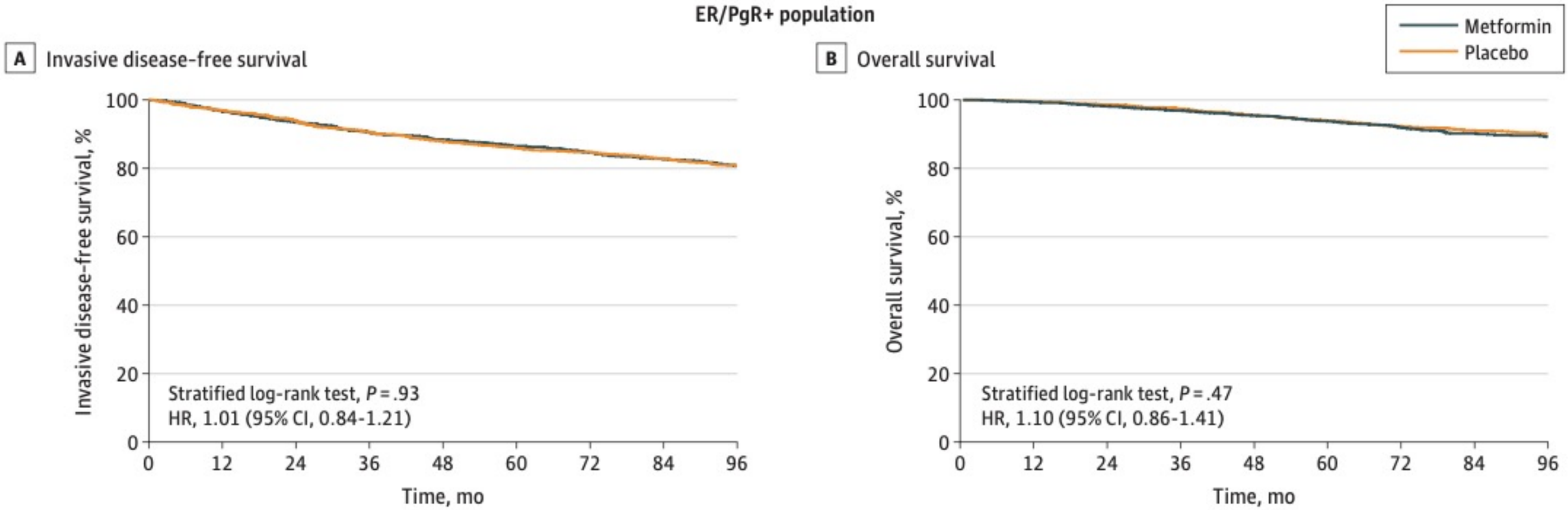
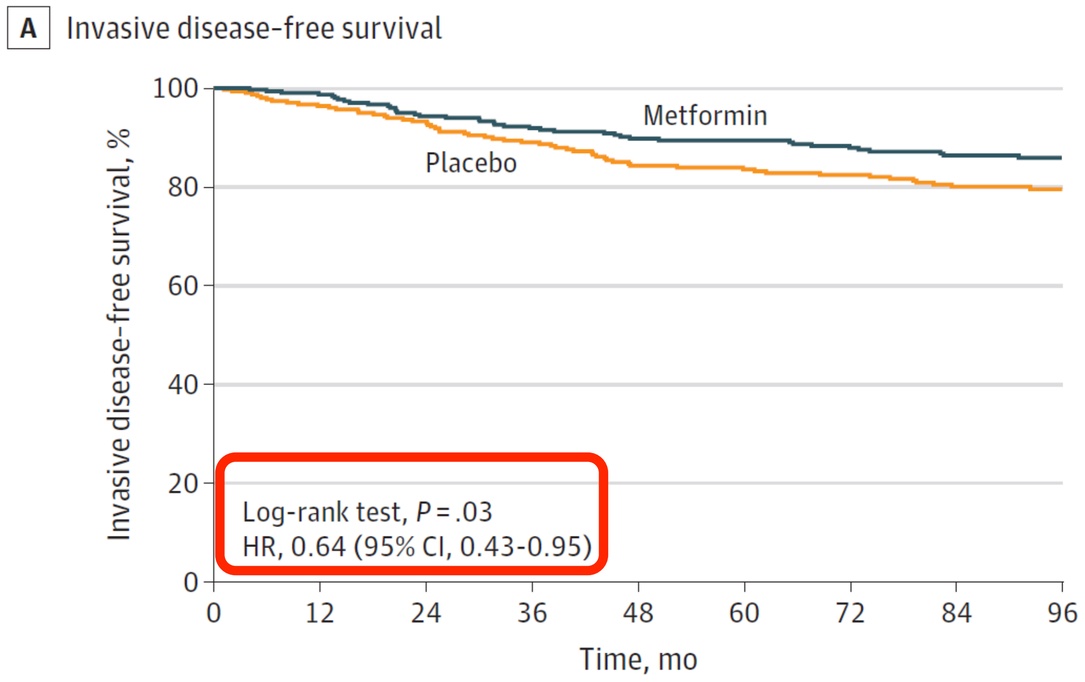
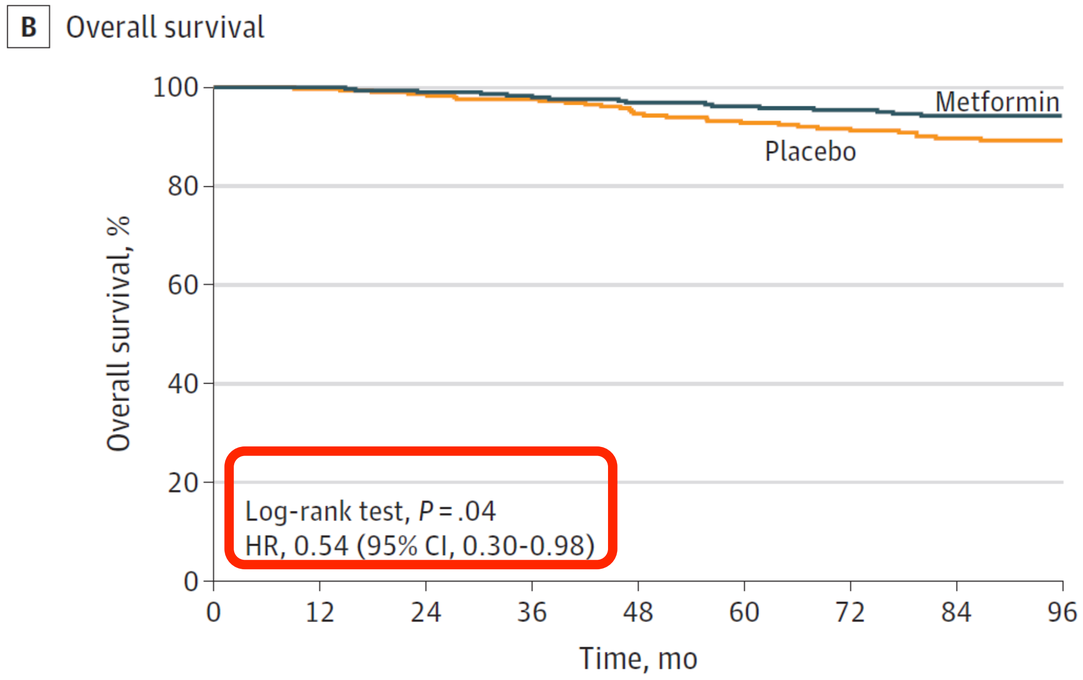
RESULTADOS

Sin diferencias significativas en el grupo PgR+



RESULTADOS





LIMITACIONES
Estudio en mujeres norteamericanas de raza blanca
No se puede extrapolar a pacientes diabéticas

CONCLUSIONS AND RELEVANCE Among patients with high-risk operable breast cancer without diabetes, the addition of metformin vs placebo to standard breast cancer treatment did not significantly improve invasive disease-free survival.

Effect of self-monitoring of blood pressure on diagnosis of hypertension during higher-risk pregnancy

Tucker KL, et al. JAMA 2022; 327: 1656-65

La AMPA en la población general mejora el diagnóstico y tratamiento de la HTA en la población general, pero ¿y en embarazadas?
En pacientes con factores de riesgo para preeclampsia se puede necesitar un seguimiento más frecuente e incluso puede que la TA aumente rápidamente entre visitas médicas…

PACIENTES Y MÉTODOS

Estudio randomizado (no ciego) con 2441 embarazadas con alto riesgo de preeclampsia en 15 hospitales británicos entre 2018-2019.
Definición de alto riesgo (guías UK):

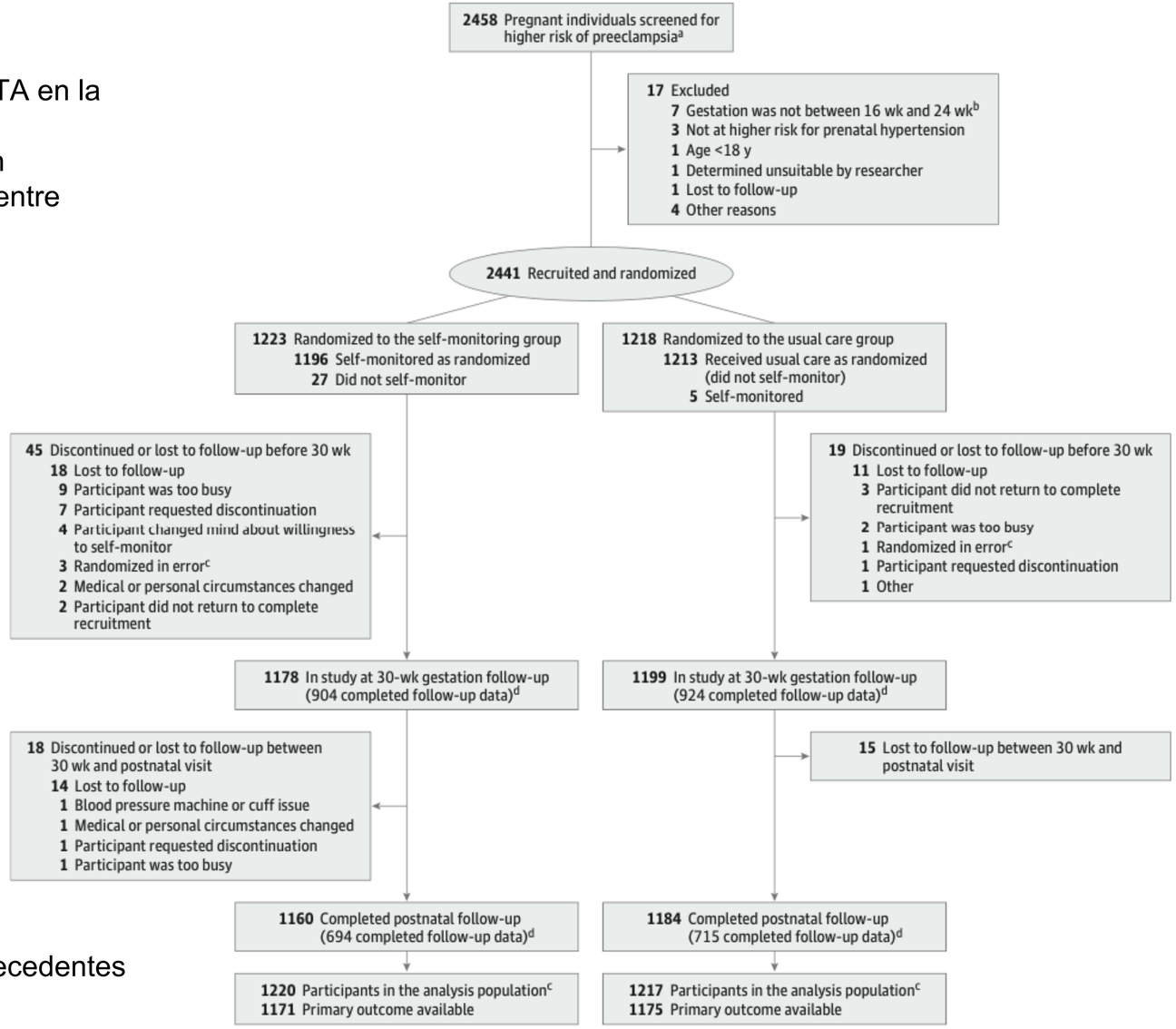
- Edad mayor de 40 años y nulípara (o embarazo previo 10 años antes)
- Historia familiar de preeclampsia
- Antecedente de preeclampsia o HTA gestacional
- IMC > 30
- Enfermedad renal crónica
- Diabetes gestacional
- Embarazo gemelar
- Enfermedad autoinmune de base (LES o SAF).

Criterios de exclusión: HTA previa al embarazo.
Randomización 1:1 AMPA y telemonitorización vs seguimiento habitual.

Definición de HTA: 140/90 en 2 o más tomas separadas 1 semana.

RESULTADOS

Características demográficas similares.
Edad media: 33 años. 60% nulíparas; un 36% con IMC>30 y el 17% con antecedentes de HTA/preeclampsia durante el embarazo.



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RESULTADOS

Table 2. Primary Outcome: Time From Randomization to Diagnosis of Elevated Sustained Blood Pressure

	Self-monitoring group	Usual care group	Difference (95% CI)	*P* value[a]
Participants with primary outcome data	1171	1175		
Clinic hypertension, No. (%)[b]	179 (15.3)	184 (15.7)	0.0 (−3 to 2)[c]	.75
Time to clinic hypertension, d				
Mean (SD)	104.3 (32.6)	106.2 (32.0)	−1.6 (−8.1 to 4.9)	.64
Median (IQR)	109 (90 to 127)	115 (90 to 129)		

Sin diferencias significativas

Table 3. Selected Secondary Maternal and Perinatal Outcomes by Randomized Group[a]

	No./total (%)		Adjusted absolute difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[b]	*P* value for treatment effect
	Self-monitoring group	Usual care group			
Maternal					
Severe hypertension	69/1171 (6.0)	57/1175 (4.9)	1.09 (−0.94 to 3.12)	1.22 (0.87 to 1.70)	.25
Preeclampsia	51/1209 (4.2)	51/1209 (4.2)	0.01 (−1.84 to 1.85)	1.00 (0.66 to 1.51)	>.99
≥1 Serious maternal complications[c]	15/1209 (1.2)	19/1209 (1.6)			
Perinatal					
Gestation at delivery, median (IQR), wk	39.3 (38.1 to 40.4) [1190]	39.3 (38.0 to 40.4) [1185]	0.14 (−0.01 to 0.30)[d]		
Stillbirth	5/1260 (0.4)	3/1248 (0.2)			
Neonatal death within 7 d	2/1248 (0.2)	0/1240			
Small for gestational age (<10th percentile)	104/1249 (8.3)	87/1235 (7.0)	1.10 (−1.09 to 3.29)	1.15 (0.87 to 1.53)	.32
Infant admitted to neonatal intensive care unit	161/1248 (12.9)	163/1240 (13.1)	−0.64 (−3.34 to 2.05)	0.95 (0.77 to 1.17)	.63

LIMITACIONES

26% de pacientes con preeclampsia tenían cifras normales en AMPA

27% de las pacientes del grupo control se monitorizaban las cifras de TA antes del estudio

Cifra de corte utilizada 140/90

RESULTADOS

Table 2. Primary Outcome: Time From Randomization to Diagnosis of Elevated Sustained Blood Pressure

	Self-monitoring group	Usual care group	Difference (95% CI)	*P* value[a]
Participants with primary outcome data	1171	1175		
Clinic hypertension, No. (%)[b]	179 (15.3)	184 (15.7)	0.0 (−3 to 2)[c]	
Time to clinic hypertension, d				
Mean (SD)	104.3 (32.6)	106.2 (4[illegible]		
Median (IQR)	109 (90 to 127)			

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CONCLUSIONS AND RELEVANCE Among pregnant individuals at higher risk of preeclampsia, blood pressure self-monitoring with telemonitoring, compared with usual care, did not lead to significantly earlier clinic-based detection of hypertension.

26% de p
tenían cifr

27% de las [illegible]ntes del grupo control se monitorizaban las cifras de TA antes del estudio

Cifra de corte utilizada 140/90

	[illegible] group	Usual care group	Adjusted absolute difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[b]	*P* value for treatment effect
	69/1171 (6.0)	57/1175 (4.9)	1.09 (−0.94 to 3.12)	1.22 (0.87 to 1.70)	.25
[illegible]mpsia	51/1209 (4.2)	51/1209 (4.2)	0.01 (−1.84 to 1.85)	1.00 (0.66 to 1.51)	>.99
≥1 Serious maternal complications[c]	15/1209 (1.2)	19/1209 (1.6)			
Perinatal					
Gestation at delivery, median (IQR), wk	39.3 (38.1 to 40.4) [1190]	39.3 (38.0 to 40.4) [1185]	0.14 (−0.01 to 0.30)[d]		
Stillbirth	5/1260 (0.4)	3/1248 (0.2)			
Neonatal death within 7 d	2/1248 (0.2)	0/1240			
Small for gestational age (<10th percentile)	104/1249 (8.3)	87/1235 (7.0)	1.10 (−1.09 to 3.29)	1.15 (0.87 to 1.53)	.32
Infant admitted to neonatal intensive care unit	161/1248 (12.9)	163/1240 (13.1)	−0.64 (−3.34 to 2.05)	0.95 (0.77 to 1.17)	.63

Effect of self-monitoring of blood pressure on blood pressure control in pregnant individuals with chronic or gestational hypertension

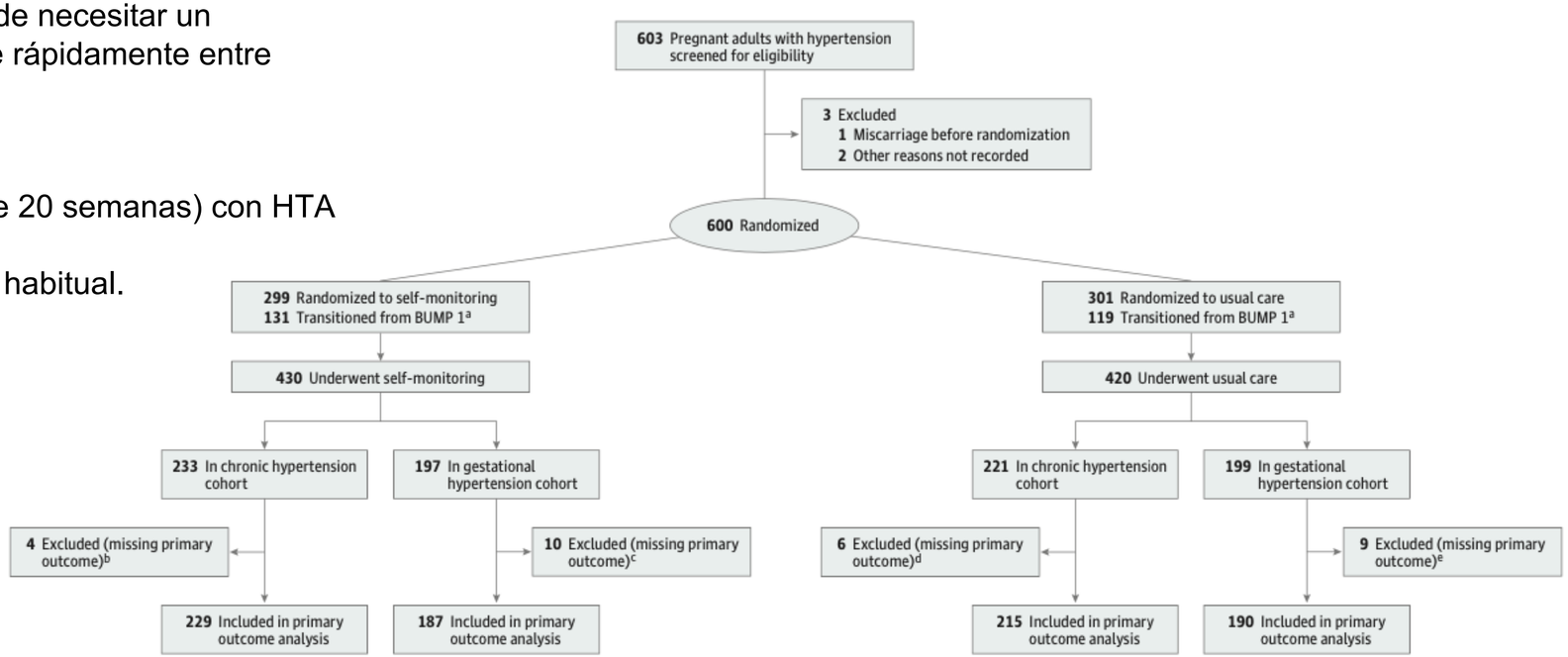
Chappell LC, et al. JAMA 2022; 327: 1666-78

La AMPA en la población general mejora el diagnóstico y tratamiento de la HTA en la población general; pero, ¿y en embarazadas?
En pacientes con factores de riesgo para preeclampsia se puede necesitar un seguimiento más frecuente e incluso puede que la TA aumente rápidamente entre visitas médicas…

PACIENTES Y MÉTODOS

Estudio randomizado (no ciego) con 850 embarazadas (más de 20 semanas) con HTA gestacional. (TA>140/90) o HTA previa al embarazo.
Randomización 1:1 AMPA y telemonitorización vs seguimiento habitual.
Realizan AMPA diario

Endpoint primario: diferencia en cifra media de TA sistólica.



RESULTADOS

Características demográficas similares.
Edad media HTA crónica: 36 años y un 66% realizaban AMPA antes de entrar en el estudio
Edad media HTA gestacional: 34 años (semana 33 de embarazo) y un 43% realizaban AMPA previamente.

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Chappell LC, et al. JAMA 2022; 327: 1666-78

RESULTADOS

Table 2. Primary Outcome: Mean Blood Pressure for Participants With Chronic Hypertension and Gestational Hypertension

	Self-monitoring	Usual care	Adjusted mean difference (95% CI)	*P* value
Chronic hypertension				
Primary outcome available, No. (%)[a]	229 (98.3)	215 (97.3)		
Blood pressure, mean (SD), mm Hg				
Systolic[b]	133.8 (10.3)	133.6 (11.1)	0.03 (−1.73 to 1.79)[c]	.97
Diastolic	84.0 (7.4)	84.3 (7.9)	−0.03 (−1.28 to 1.22)	.96
Gestational hypertension				
Primary outcome available, No. (%)[a]	187 (94.9)	190 (95.5)		
Blood pressure, mean (SD), mm Hg				
Systolic	137.6 (12.1)	137.2 (10.8)	−0.03 (−2.29 to 2.24)[d]	.98
Diastolic	86.1 (7.8)	86.3 (7.7)	−0.35 (−1.77 to 1.06)	.63

Sin diferencias significativas en endpoint primario

Maternal outcomes, No.
No. of blood pressure measurements[b]
No. (proportion) of days with systolic blood pressure >140 mm Hg
Gestation at birth, median (IQR), wk
Maternal outcomes for those with primary outcome only, No.
Severe hypertension[c]
Preeclampsia
Received a blood transfusion[d]
Maternal death[d]
Maternal outcomes for those delivering after 24 wk, No.
Spontaneous onset of labor
Infant outcomes (all births), No.
Spontaneous vaginal birth
Stillbirths[d]
Infants <10th birth weight centile
Birth weight centile
Infant outcomes (live births only), No.
Neonatal unit admission
Early neonatal deaths
Days of neonatal unit stay for those admitted, median (IQR)

Sin diferencias significativas en complicaciones embarazo

LIMITACIONES

¿Mejorar la técnica/adiestramiento para el AMPA y telemonitorización podría influir en los resultados?

RESULTADOS

Table 2. Primary Outcome: Mean Blood Pressure for Participants With Chronic Hypertension and Gestational Hypertension

	Self-monitoring	Usual care	Adjusted mean difference (95% CI)	*P* value
Chronic hypertension				
Primary outcome available, No. (%)[a]	229 (98.3)	215 (97.3)		
Blood pressure, mean (SD), mm Hg				
Systolic[b]	133.8 (10.3)	133.6 (11.1)	0.03 (−1.73 to 1.79)[c]	.97
Diastolic	84.0 (7.4)	84.3 (7.9)	−0.03 (−1.28 to 1.22)	.96
Gestational hypertension				
Primary outcome available, No. (%)[a]	187 (94.9)	190 (95.5)		
Blood pressure, mean (SD), mm Hg				
Systolic	137.6 (12.1)	137.2 (10.8)		
Diastolic	86.1 (7.8)			

Sin diferencias significativas en end

CONCLUSIONS AND RELEVANCE Among pregnant individuals with chronic or gestational hypertension, blood pressure self-monitoring with telemonitoring, compared with usual care, did not lead to significantly improved clinic-based blood pressure control.

...cias significativas en complicaciones embarazo

¿Mejo... para el AMPA y telemonitorización podría ...ultados?

Maternal outcomes, No.
No. of blood pressure measurements[b]
No. (proportion) of days with systolic blood pressure >140 mm Hg
Gestation at birth, median (IQR), wk
Maternal outcomes for those with primary outcome only, No.
Severe hypertensi...
Pre...
...es for those delivering ...wk, No.
Spontaneous onset of labor
Infant outcomes (all births), No.
Spontaneous vaginal birth
Stillbirths[d]
Infants <10th birth weight centile
Birth weight centile
Infant outcomes (live births only), No.
Neonatal unit admission
Early neonatal deaths
Days of neonatal unit stay for those admitted, median (IQR)

Treatment for mild chronic hypertension during pregnancy

Tita AT, et al. New Engl J Med 2022. DOI: 10.1056/NEJMoa2201295

Definición: TA sistólica>140 mmHg y/o diastólica>90 mmHg antes del embarazo, o bien antes de la semana 20 o HTA diagnosticada posteriormente que se mantiene después del puerperio.
HTA gestacional o preeclampsia: cifras tensionales normales después…
Vigilancia regular, AAS a partir de la semana 12 (prevención preeclampsia) y controles en consulta.

Aumento del riesgo de preeclampsia (x3 o x5), desprendimiento de placenta, parto prematuro o mortalidad perinatal.
Sin embargo el tratamiento con antihipertensivos es controvertido: reduce la TA pero no se ha demostrado que mejore otros parámetros perinatales y se asocia con bajo peso al nacer

¿Cuándo tratar la TA? Consenso por encima de 160/110 mmHg

PACIENTES Y MÉTODOS

Estudio multicéntrico, randomizado, open-label.
Mujeres embarazadas con HTA crónica leve antes de la semana 23.
Criterios de exclusión:
- HTA en tratamiento con más de 1 antihipertensivo (por alto riesgo de HTA grave)
- HTA secundaria
- Otras patologías obstétricas que pueden aumentar el riesgo fetal
- Contraindicaciones para los fármacos antihipertensivos del estudio

Randomización 1: 1 → grupo control vs tratamiento (labetalol, nifepidino, amlodipino o metildopa).

Endpoint primario: compuesto preeclampsia, parto pretérmino (antes de la 35s), desprendimiento de placenta, mortalidad fetal/neonatal.
Endpoint de seguridad: bajo peso al nacer (< percentil 10).

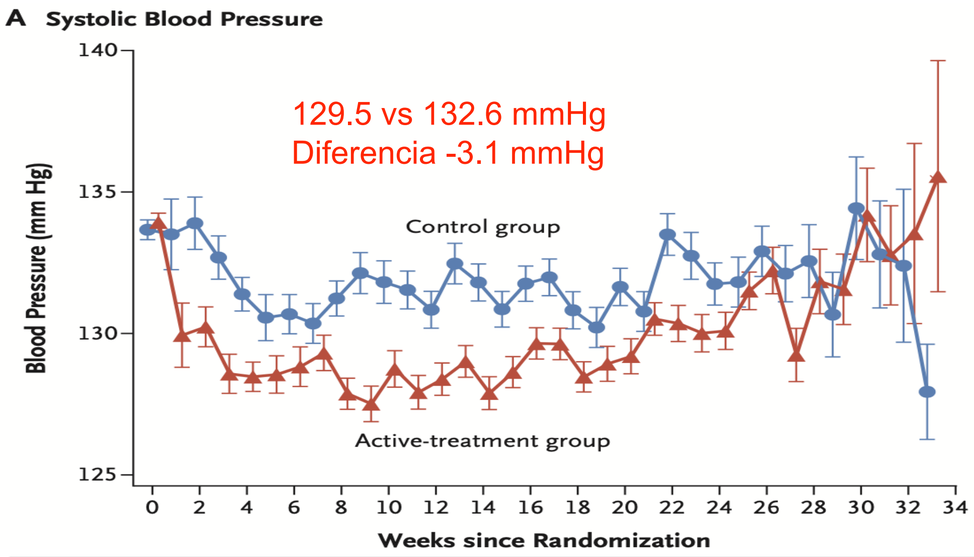
RESULTADOS

Grupos similares.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Active Treatment (N=1208)	Control (N=1200)
Age — yr	32.3±5.6	32.3±5.8
Race or ethnic group — no. (%)†		
Non-Hispanic White	347 (28.7)	326 (27.2)
Non-Hispanic Black	574 (47.5)	570 (47.5)
Hispanic	238 (19.7)	250 (20.8)
Other	49 (4.1)	54 (4.5)
Mother's type of insurance — no. (%)		
Government-assisted insurance or Medicaid	673 (55.7)	656 (54.7)
Private insurance	459 (38.0)	463 (38.6)
None	60 (5.0)	65 (5.4)
Missing data	16 (1.3)	16 (1.3)
Type of chronic hypertension — no. (%)		
Newly diagnosed	263 (21.8)	258 (21.5)
Diagnosed and receiving medication	677 (56.0)	681 (56.8)
Diagnosed and not receiving medication	268 (22.2)	261 (21.8)
Blood pressure — mm Hg		
Systolic	134.3±12.7	133.7±12.4
Diastolic	83.9±9.5	83.4±9.6
Previous pregnancy — no. (%)	1007 (83.4)	989 (82.4)
Body-mass index‡		
Mean	37.7±10.0	37.5±9.6
Distribution — no. (%)		
<30	295 (24.4)	259 (21.6)
30 to <40	460 (38.1)	517 (43.1)
≥40	434 (35.9)	402 (33.5)
Gestational age <14 wk — no. (%)	496 (41.1)	481 (40.1)
Coexisting illness or lifestyle factor — no. (%)		
Diabetes mellitus	191 (15.8)	189 (15.8)
Current smoker	92 (7.6)	82 (6.8)
Aspirin use	539 (44.6)	536 (44.7)

RESULTADOS: Tratamientos recibidos: 61% labetalol y 35.6% nifedipino



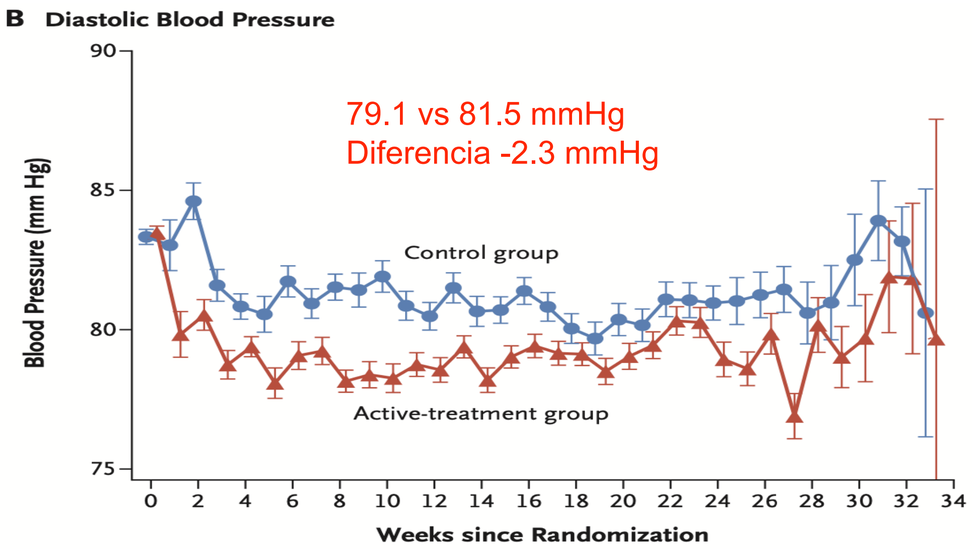


Table 2. Primary and Safety Outcomes.

NNT 14

Outcome	Imputation Analysis (N=2408)*		Complete-Case Analysis (N=2325)†			
	Adjusted Risk Ratio (95% CI)	P Value	Active Treatment	Control	Risk Ratio (95% CI)	P Value
			no./total no. (%)			
Primary composite outcome	0.82 (0.74–0.92)	<0.001	353/1170 (30.2)	427/1155 (37.0)	0.82 (0.73–0.92)	<0.001
Preeclampsia with severe features	0.80 (0.70–0.92)		272/1170 (23.3)	336/1155 (29.1)	0.80 (0.70–0.92)	
Medically indicated preterm birth at <35 wk	0.73 (0.60–0.89)		143/1170 (12.2)	193/1155 (16.7)	0.73 (0.60–0.89)	
Placental abruption	0.88 (0.49–1.59)		20/1170 (1.7)	22/1155 (1.9)	0.90 (0.49–1.64)	
Fetal or neonatal death at <28 days	0.81 (0.54–1.22)		41/1170 (3.5)	50/1155 (4.3)	0.81 (0.54–1.21)	
Safety outcome						
Small for gestational age						
<10th percentile	1.04 (0.82–1.31)	0.76	128/1146 (11.2)	117/1124 (10.4)	1.07 (0.85–1.36)	0.56
<5th percentile	0.89 (0.62–1.26)	0.51	58/1146 (5.1)	62/1124 (5.5)	0.92 (0.65–1.30)	0.63

RESULTADOS: Análisis de eventos maternales y neonatales

Table 3. Maternal Outcomes.* — **Sin grandes diferencias**

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite cardiovascular complications — no. (%)	25 (2.1)	33 (2.8)	0.75 (0.45 to 1.26)
Maternal death	1 (0.1)	2 (0.2)	0.50 (0.05 to 5.47)
Heart failure	1 (0.1)	1 (0.1)	0.99 (0.06 to 15.9)
Stroke	0	0	NA
Myocardial infarction or angina	0	0	NA
Pulmonary edema	5 (0.4)	11 (0.9)	0.45 (0.16 to 1.30)
ICU admission or intubation	12 (1.0)	16 (1.3)	0.75 (0.35 to 1.57)
Encephalopathy	1 (0.1)	0	1.00 (1.00 to 1.00)
Renal failure	9 (0.8)	14 (1.2)	0.64 (0.28 to 1.47)
Severe hypertension — no. (%)	436 (36.1)	531 (44.3)	0.82 (0.74 to 0.90)
Any preeclampsia — no. (%)	295 (24.4)	373 (31.1)	0.79 (0.69 to 0.89)
Severe hypertension plus proteinuria	189 (15.7)	215 (17.9)	0.87 (0.73 to 1.04)
Eclampsia	0	1 (0.1)	NA
HELLP	0	3 (0.3)	NA
Hypertension plus end-organ dysfunction	136 (11.3)	181 (15.1)	0.75 (0.61 to 0.92)
Nonsevere preeclampsia	23 (1.9)	37 (3.1)	0.62 (0.37 to 1.03)
Worsening chronic hypertension — no. (%)	132 (10.9)	156 (13.0)	0.84 (0.68 to 1.04)
Mean blood pressure during prenatal visits — mm Hg‡			
Systolic	129.5±10.0	132.6±10.1	−3.11 (−3.95 to 2.28)
Diastolic	79.1±7.4	81.5±8.0	−2.33 (−2.97 to 0.04)
Gestational age at delivery — wk§	36.6±4.3	36.3±5.1	0.24 (−0.15 to 0.62)
Cesarean delivery — no. (%)	592 (49.0)	582 (48.5)	1.01 (0.93 to 1.10)
Any blood transfusion — no. (%)	46 (3.8)	53 (4.4)	0.86 (0.59 to 1.27)

Table 4. Neonatal Outcomes.* — **Sin grandes diferencias**

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite of severe neonatal complications — no. (%)	24 (2.0)	31 (2.6)	0.77 (0.45 to 1.30)
Bronchopulmonary dysplasia	8 (0.7)	14 (1.2)	0.57 (0.24 to 1.35)
Retinopathy of prematurity	16 (1.3)	20 (1.7)	0.79 (0.41 to 1.53)
Necrotizing enterocolitis	2 (0.2)	2 (0.2)	0.99 (0.14 to 7.06)
Intraventricular hemorrhage, grade 3 or 4	3 (0.3)	4 (0.3)	0.75 (0.17 to 3.32)
Preterm birth at <37 wk — no. (%)	332 (27.5)	377 (31.4)	0.87 (0.77 to 0.99)
Birth weight <2500 g — no. (%)	232 (19.2)	277 (23.1)	0.83 (0.71 to 0.97)
NICU admission — no. (%)	368 (30.5)	402 (33.5)	0.91 (0.81 to 1.02)
Neonatal hospital stay			
Mean no. of days‡	2.8±1.7	2.9±1.7	−0.05 (−0.18 to 0.09)§
≥3 days — no. (%)	590 (48.8)	592 (49.3)	0.98 (0.90 to 1.06)
Ponderal index — g/cm³¶	2.9±3.7	2.7±2.8	0.16 (−0.11 to 0.43)§
Head circumference — cm‖	33.3±3.0	33.0±3.2	0.31 (0.05 to 0.56)§
Placental weight — g**	466.3±177.6	464.6±175.6	1.67 (−17.57 to 20.91)§
Hypoglycemia — no. (%)	191 (15.8)	195 (16.3)	0.97 (0.81 to 1.17)
Bradycardia — no. (%)	31 (2.6)	35 (2.9)	0.88 (0.55 to 1.42)
Hypotension — no. (%)	7 (0.6)	16 (1.3)	0.43 (0.18 to 1.05)
Any respiratory support — no. (%)	219 (18.1)	243 (20.3)	0.90 (0.76 to 1.06)
Respiratory distress syndrome — no. (%)	149 (12.3)	171 (14.3)	0.87 (0.71 to 1.06)
Transient tachypnea — no. (%)	70 (5.8)	63 (5.3)	1.10 (0.79 to 1.54)
Seizures — no. (%)	3 (0.3)	1 (0.1)	2.98 (0.31 to 28.6)
Hyperbilirubinemia — no. (%)	266 (22.0)	283 (23.6)	0.93 (0.81 to 1.08)
Apgar score of <7 at 5 min — no. (%)††	68 (5.6)	80 (6.7)	0.84 (0.62 to 1.16)
Sepsis — no. (%)			
Suspected or proven	138 (11.4)	163 (13.8)	0.84 (0.68 to 1.04)
Proven	21 (1.7)	34 (2.8)	0.61 (0.36 to 1.05)

RESULTADOS: Análisis de eventos maternales y neonatales

Table 3. Maternal Outcomes.* — **Sin grandes diferencias**

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite cardiovascular complications — no. (%)	25 (2.1)	33 (2.8)	0.75 (0.45 to 1.26)
Maternal death	1 (0.1)	2 (0.2)	0.50 (0.05 to 5.47)
Heart failure	1 (0.1)	1 (0.1)	0.99 (0.06 to 15.9)
Stroke	0	0	NA
Myocardial infarction or angina	0	0	NA
Pulmonary edema	5 (0.4)	11 (0.9)	0.45 (0.16 to 1.30)
ICU admission or intubation	12 (1.0)	16 (1.3)	0.75 (0.35 to 1.57)
Encephalopathy	1 (0.1)	0	1.00 (1.00 to 1.00)
Renal failure	9 (0.8)	14 (1.2)	0.64 [illegible]
Severe hypertension — no. (%)	436 (36.1)	[illegible]	[illegible]
Any preeclampsia — no. (%)	[illegible]	[illegible]	[illegible]
Severe hypertension plus proteinuria	[illegible]	[illegible]	[illegible]
Eclampsia	[illegible]	[illegible]	[illegible]
HELLP	[illegible]	[illegible]	[illegible]
Hypertension plus end-organ dysfunction	[illegible]	[illegible]	[illegible]
Nonsevere preeclampsia	[illegible]	[illegible]	[illegible]
Worsening chronic hypertension — no. (%)	[illegible]	[illegible]	[illegible] (0.68 to 1.04)
Mean blood pressure during prenatal visits — mm Hg‡			
Systolic	129.5±10.0	132.6±10.1	−3.11 (−3.95 to 2.28)
Diastolic	79.1±7.4	81.5±8.0	−2.33 (−2.97 to 0.04)
Gestational age at delivery — wk§	36.6±4.3	36.3±5.1	0.24 (−0.15 to 0.62)
Cesarean delivery — no. (%)	592 (49.0)	582 (48.5)	1.01 (0.93 to 1.10)
Any blood transfusion — no. (%)	46 (3.8)	53 (4.4)	0.86 (0.59 to 1.27)

Table 4. Neonatal Outcomes.* — **Sin grandes diferencias**

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite of severe neonatal complications — no. (%)	24 (2.0)	31 (2.6)	0.77 (0.45 to 1.30)
Bronchopulmonary dysplasia	8 (0.7)	14 (1.2)	0.57 (0.24 to 1.35)
Retinopathy of prematurity	16 (1.3)	20 (1.7)	0.79 (0.41 to 1.53)
Necrotizing enterocolitis	2 (0.2)	2 (0.2)	0.99 (0.14 to 7.06)
Intraventricular hemorrhage, grade 3 or 4	3 (0.3)	4 (0.3)	0.75 (0.17 to 3.32)
Preterm birth at <37 wk — no. (%)	332 (27.5)	377 (31.4)	0.87 (0.77 to 0.99)
Birth weight <2500 g — no. (%)	[illegible]	277 (23.1)	0.83 (0.71 to 0.97)
NICU admission — no. (%)	[illegible]	402 (33.5)	0.91 (0.81 to 1.02)
[illegible]	[illegible]		
[illegible]	[illegible]	2.9±1.7	−0.05 (−0.18 to 0.09)§
[illegible]	[illegible]	592 (49.3)	0.98 (0.90 to 1.06)
[illegible]	[illegible]	2.7±2.8	0.16 (−0.11 to 0.43)§
[illegible]	[illegible]	33.0±3.2	0.31 (0.05 to 0.56)§
[illegible]	[illegible]	464.6±175.6	1.67 (−17.57 to 20.91)§
[illegible]	[illegible]	195 (16.3)	0.97 (0.81 to 1.17)
[illegible]	31 (2.6)	35 (2.9)	0.88 (0.55 to 1.42)
[illegible] — no. (%)	7 (0.6)	16 (1.3)	0.43 (0.18 to 1.05)
Any respiratory support — no. (%)	219 (18.1)	243 (20.3)	0.90 (0.76 to 1.06)
Respiratory distress syndrome — no. (%)	149 (12.3)	171 (14.3)	0.87 (0.71 to 1.06)
Transient tachypnea — no. (%)	70 (5.8)	63 (5.3)	1.10 (0.79 to 1.54)
Seizures — no. (%)	3 (0.3)	1 (0.1)	2.98 (0.31 to 28.6)
Hyperbilirubinemia — no. (%)	266 (22.0)	283 (23.6)	0.93 (0.81 to 1.08)
Apgar score of <7 at 5 min — no. (%)††	68 (5.6)	80 (6.7)	0.84 (0.62 to 1.16)
Sepsis — no. (%)			
Suspected or proven	138 (11.4)	163 (13.8)	0.84 (0.68 to 1.04)
Proven	21 (1.7)	34 (2.8)	0.61 (0.36 to 1.05)

CONCLUSIONS

In pregnant women with mild chronic hypertension, a strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes than a strategy of reserving treatment only for severe hypertension, with no increase in the risk of small-for-gestational-age birth weight. (Funded by the National Heart, Lung, and Blood Institute; CHAP ClinicalTrials.gov number, NCT02299414.)

¡Muchas gracias!

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Y otras sesiones que se comentaron la semana pasada…

Acetazolamide in acute decompensated heart failure with volumen overload

Mullens W, et al. New Engl J Med 2022. **DOI: 10.1056/NEJMoa2203094**

DOSE: Sólo el 15% de pacientes con IC resuelven por completo la congestión a los 3 días.
ADHERE: 20% de altas hospitalarias por IC mantienen ganancia de peso respecto al basal.
Bloqueo de la nefrona a distintos niveles > monoterapia, pero ¿dosis, vía, calendario ajuste?

PACIENTES Y MÉTODOS

Estudio randomizado, doble ciego y multicéntrico en hospitales de Bélgica
Incluyen pacientes con descompensación de IC y proBNP>1000
Criterios de exclusión:

- Tratamiento con diuréticos de túbulo proximal, incluidos sGLT2,
- TA sistólica inferior a 90 mmHg
- FG menor de 20 ml/min
- Tratamiento previo con más de 80 mg de Furosemida.

Randomización 1:1 Acetazolamida 500 mg iv 3 días vs placebo, añadido a diruéticos de asa
Además asocian furosemida a dosis doble de la ambulatoria repartida cada 12 horas.
Todos los pacientes sondados y si a las 30 horas la diuresis era < 3.5 litros y mantenían datos de congestión se aumentaba la dosis de diuréticos de asa.
Score de congestión: 0-10 en función de edemas (4), derrame pleural (3) y/o ascitis (3).

Seguimiento de 3 meses para valorar mortalidad y reingresos por IC
Endpoint primario: resolución completa de la congestión a los 3 días.

RESULTADOS

N=519 pacientes incluidos entre 2018-2022
Grupos con características clínicas similares.
proBNP medio de 6173.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=260)	Acetazolamide (N=259)	Total (N=519)
Age — yr	78.5±8.8	77.9 ±9.0	78.2±8.9
Male sex — no. (%)	155 (59.6)	170 (65.6)	325 (62.6)
White race — no. (%)†	[illegible]	[illegible]	[illegible]
Heart rate — beats/min	77±18	79±19	78±18
Blood pressure — mm Hg			
Systolic	127±22	126±20	127±21
Diastolic	73±13	72±13	72±13
Weight — kg	[illegible]	[illegible]	[illegible]
Median congestion score at baseline (IQR)‡	4 (3–6)	4 (3–5)	4 (3–6)
Components of congestion score — no. (%)			
Edema§	241 (92.7)	237 (91.5)	478 (92.1)
Pleural effusion	143 (55.0)	130 (50.2)	273 (52.6)
Ascites	25 (9.6)	21 (8.1)	46 (8.9)
Median home maintenance dose of furosemide equivalent (IQR) — mg	60 (40–100)	80 (40–120)	60 (40–100)
Left ventricular ejection fraction			
Mean — %	43±15	43±15	43±15
≤40% — no. (%)	111 (42.7)	113 (43.6)	224 (43.2)
Median NT-proBNP (IQR) — pg/ml	6483 (3262–11,839)	5600 (3034–10,100)	6173 (3068–10,896)
NYHA functional class — no. (%)			
II	35 (13.5)	31 (12.0)	66 (12.7)
III	148 (56.9)	148 (57.1)	296 (57.0)
IV	77 (29.6)	80 (30.9)	157 (30.3)
Ischemic cause — no. (%)	[illegible]	[illegible]	[illegible]
Serum hemoglobin — g/dl	11.9±2.0	11.9±2.0	11.9±2.0
Sodium — mmol/liter	140±4	139±4	139±4
Median serum creatinine (IQR) — mg/dl	1.5 (1.2–1.9)	1.5 (1.2–2.0)	1.5 (1.2–1.9)
Estimated GFR			
Median (IQR) — ml/min/1.73 m²	38 (29–51)	40 (30–52)	39 (29–52)
<60 ml/min/1.73 m² — no. (%)	215 (82.7)	209 (80.7)	424 (81.7)
Coexisting conditions — no. (%)			
History of atrial fibrillation	189 (72.7)	187 (72.2)	376 (72.4)
Diabetes	133 (51.2)	112 (43.2)	245 (47.2)
Hypertension	207 (79.6)	182 (70.3)	389 (75.0)
Treatment — no. (%)			
ACE inhibitor, ARB, or ARNI	140 (53.8)	130 (50.2)	270 (52.0)
Beta-blocker	212 (81.5)	207 (79.9)	419 (80.7)
Mineralocorticoid receptor antagonist	103 (39.6)	113 (43.6)	216 (41.6)
Loop diuretic	260 (100.0)	259 (100.0)	519 (100.0)
Implantable cardioverter–defibrillator	41 (15.8)	38 (14.7)	79 (15.2)
Cardiac-resynchronization therapy	25 (9.6)	36 (13.9)	61 (11.8)

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RESULTADOS

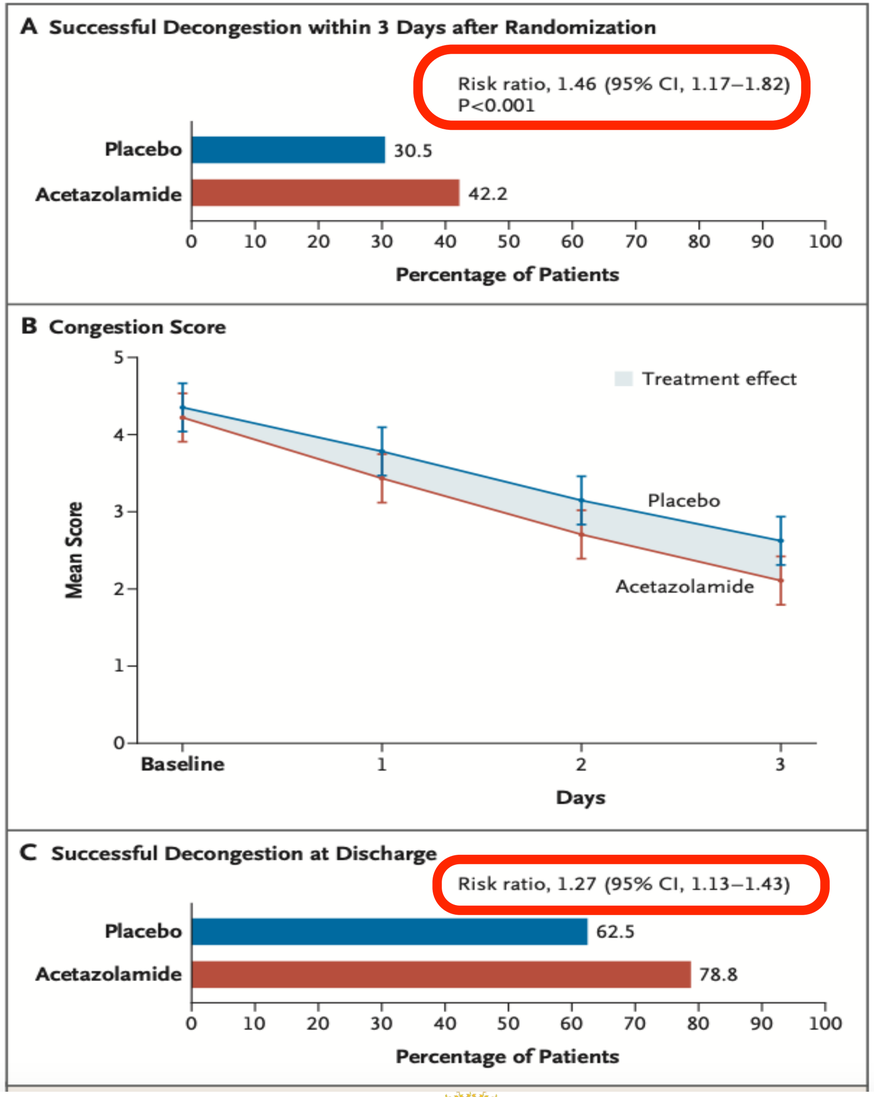


Table 2. Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse Events.*

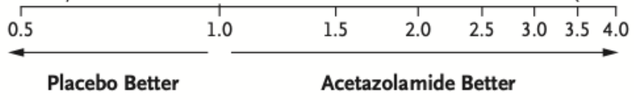
Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Primary end point				
Successful decongestion within 3 days after randomization — no. (%)†	79 (30.5)	108 (42.2)	Risk ratio, 1.46 (1.17–1.82)	<0.001
Secondary end points				
Duration of hospital stay (95% CI) — days‡	9.9 (9.1–10.8)	8.8 (8.0–9.5)	0.89 (0.81–0.98)	
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%)	72 (27.8)	76 (29.7)	Hazard ratio, 1.07 (0.78–1.48)	
Sensitivity analysis of primary end point				
Successful decongestion within 3 days after randomization, regardless of escalation of therapy — no. (%)§	86 (33.2)	115 (44.9)	Risk ratio, 1.42 (1.[illegible]	
Exploratory analysis				
Successful decongestion at discharge among patients who were alive — no./total no. (%)	145/232 (62.5)	190/241 (78.8)	Risk ratio, 1.27 (1.13–1.43)	
Death from any cause at 3 mo — no. (%)	31 (12.0)	39 (15.2)	Hazard ratio, 1.28 (0.78–2.05)	
Rehospitalization for heart failure at 3 mo — no. (%)	45 (17.4)	47 (18.4)	Hazard ratio, 1.07 (0.71–1.59)	

Sin diferencias en mortalidad/reingresos

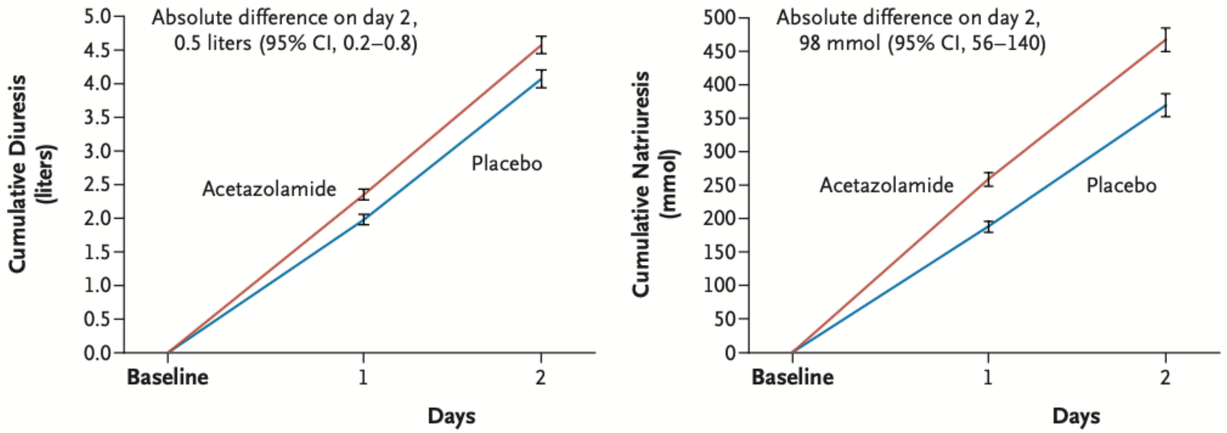
Sin diferencias significativas en cuanto a eventos adversos

RESULTADOS

Subgroup	Placebo	Acetazolamide	Risk Ratio (95% CI)
	no. of patients/total no.		
Overall	79/259	108/256	1.46 (1.17–1.82)
Age			
≤79 yr	43/130	59/132	1.36 (1.02–1.82)
>79 yr	36/129	49/124	1.56 (1.11–2.21)
Left ventricular ejection fraction			
≤40%	36/111	43/111	1.24 (0.88–1.75)
>40%	43/148	65/145	1.63 (1.22–2.19)
NT-proBNP			
≤6173 pg/ml	51/122	68/132	1.35 (1.06–1.74)
>6173 pg/ml	27/135	38/120	1.61 (1.06–2.44)
Sex			
Female	37/104	36/88	1.21 (0.86–1.71)
Male	42/155	72/168	1.67 (1.24–2.25)
Estimated GFR			
<39 ml/min/1.73 m^2	33/135	53/125	1.77 (1.25–2.50)
≥39 ml/min/1.73 m^2	46/124	55/131	1.23 (0.92–1.65)
Cause of heart failure			
Ischemic	37/113	48/118	1.35 (0.97–1.87)
Nonischemic	42/146	60/138	1.57 (1.16–2.12)
Home maintenance loop diuretic dose			
≤60 mg furosemide equivalent	42/136	67/127	1.78 (1.33–2.36)
>60 mg furosemide equivalent	37/123	41/129	1.08 (0.76–1.55)
Baseline congestion score			
≤4	60/145	82/155	1.38 (1.10–1.74)
>4	19/114	26/101	1.62 (0.96–2.73)
Atrial fibrillation			
No	20/71	31/71	1.76 (1.14–2.72)
Yes	59/188	77/185	1.35 (1.04–1.75)



Efecto sobre la diuresis y la natriuresis



LIMITACIONES

¿Generalización de resultados?
- Pacientes de raza blanca
- Historia de IC crónica en tratamiento con 40 mg o más de Furosemida

¿Resultados similares con otros diuréticos de asa?
Excluídos pacientes con tratamiento con sGLT2

CONCLUSIONS

The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion. (Funded by the Belgian Health Care Knowledge Center; ADVOR ClinicalTrials.gov number, NCT03505788.)

Dapaglifozin in heart failure with mildly reduced or preserved ejection fraction

Solomon SD, et al. New Engl J Med 2022. **DOI: 10.1056/NEJMoa2206286**

Recomendación en guías clínicas (evidencia IA) en FEVI reducida.
Datos del EMPEROR-Preserved en pacientes con FEVI preservada/ligeramente reducida

PACIENTES Y MÉTODOS

Estudio randomizado, doble ciego con 6263 pacientes con insuficiencia cardiaca y FEVI>40%
Randomización: dapaglifozina 10 mg/d vs placebo
Endpoint primario: compuesto IC (ingreso/urgencias) + mortalidad cardiovascular

RESULTADOS

Grupos con características clínicas similares.
Abandono tratamiento 14% en ambos grupos.
Duración media del seguimiento: 2.3 años

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=3131)	Placebo (N=3132)
Age — yr	71.8±9.6	71.5±9.5
Female sex — no. (%)	1364 (43.6)	1383 (44.2)
Race — no. (%)†		
Asian	630 (20.1)	644 (20.6)
Black	81 (2.6)	78 (2.5)
White	2214 (70.7)	2225 (71.0)
Other	206 (6.6)	185 (5.9)
Geographic region — no. (%)		
North America	428 (13.7)	423 (13.5)
Latin America	602 (19.2)	579 (18.5)
Europe or Saudi Arabia	1494 (47.7)	1511 (48.2)
Asia	607 (19.4)	619 (19.8)
NYHA class — no. (%)‡		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean — %	54.0±8.6	54.3±8.9
Distribution — no. (%)		
≤49%	1067 (34.1)	1049 (33.5)
50–59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
Medical history — no. (%)		
Type 2 diabetes mellitus	1401 (44.7)	1405 (44.9)
Hypertension	2755 (88.0)	2798 (89.3)
Previous left ventricular ejection fraction ≤40%	572 (18.3)	579 (18.5)
Estimated GFR — ml/min/1.73 m²	61±19	61±19

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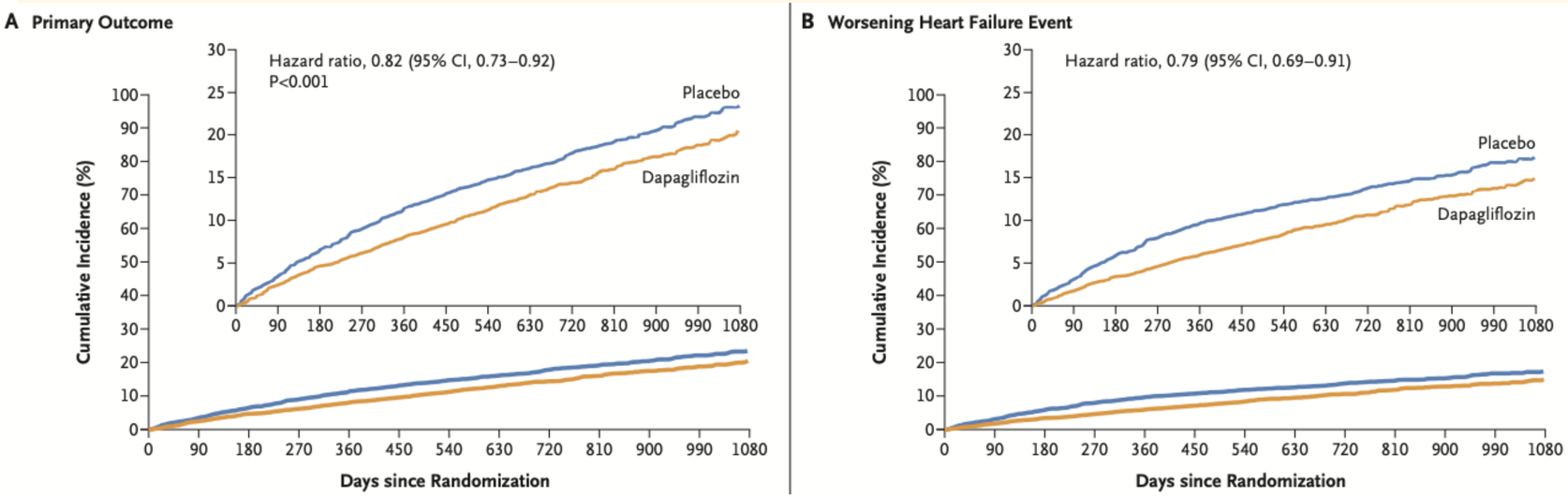
RESULTADOS

Sin diferencias en los distintos subgrupos (por FEVI, clase funcional, niveles de proBNP, FG basal, etc…

Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Sin diferencias en mortalidad

Variable	Dapagliflozin (N=3131) values	Dapagliflozin (N=3131) events/ 100 patient-yr	Placebo (N=3132) values	Placebo (N=3132) events/ 100 patient-yr	Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths†	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8¶	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA



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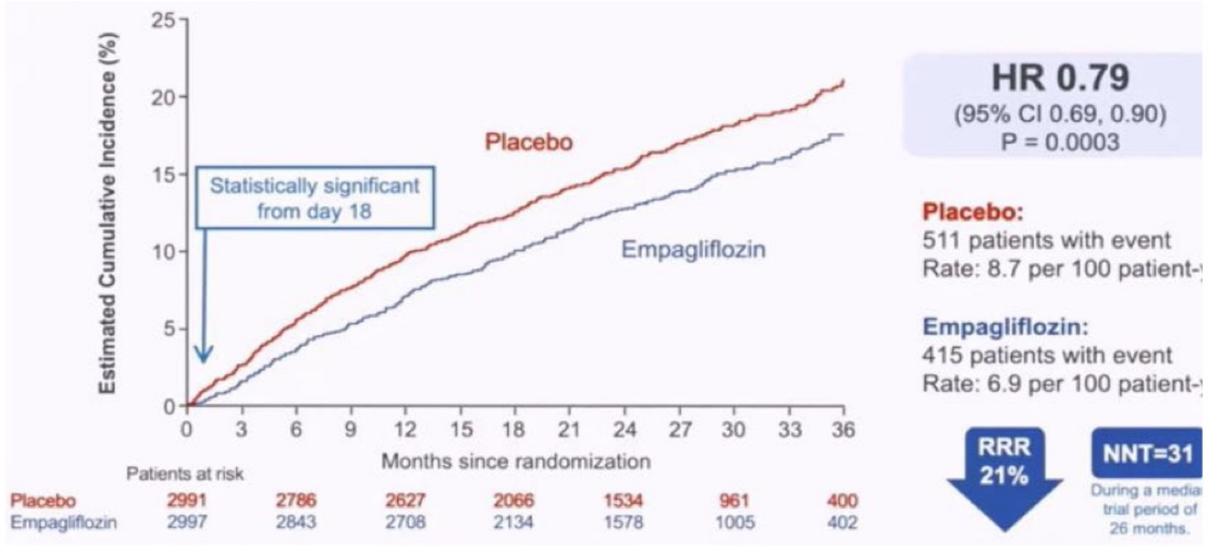
Risk for first HF hospitalization or CV death with empagliflozin vs. placebo:

HR = 0.79	HR = 0.78
With type 2 diabetes	Without type 2 diabetes



Reducción del 21%
Compuesto mortalidad cardiovascular y hospitalización por IC (NNT 31)

Efficacy Outcomes	Empagliflozin	Placebo	Hazard ratio/difference (95% confidence interval)
Death from any cause	14.1%	14.3%	1.00 (0.87-1.15)
CV death	7.3%	8.2%	0.91 (0.76-1.09)
Death or hospitalization	45.2%	47.8%	**0.92 (0.85-0.99); -2.6%**
Total* hospitalizations for any cause	2566	2768	0.93 (0.85-1.01)
Total* HF hospitalizations	407	541	**0.73 (0.61-0.88)**
1° outcome (Time to 1st HF hospitalization or CV death)	13.8%	17.1%	**0.79 (0.69-0.90); -3.3%**
1st HF hospitalization	8.6%	11.8%	**0.71 (0.60-0.83); -3.2%**
Change in KCCQ clinical summary score at 1 y	+4.5	+3.2	**+1.3 (+0.45 to +2.2)**
eGFR mean change/y	-1.25	-2.62	**+1.36 (+1.06-1.66)**

Resultados similares a los presentados con Empaglifozina (Emperor-Preserved)

Packet M. NEJM 2021

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RESULTADOS

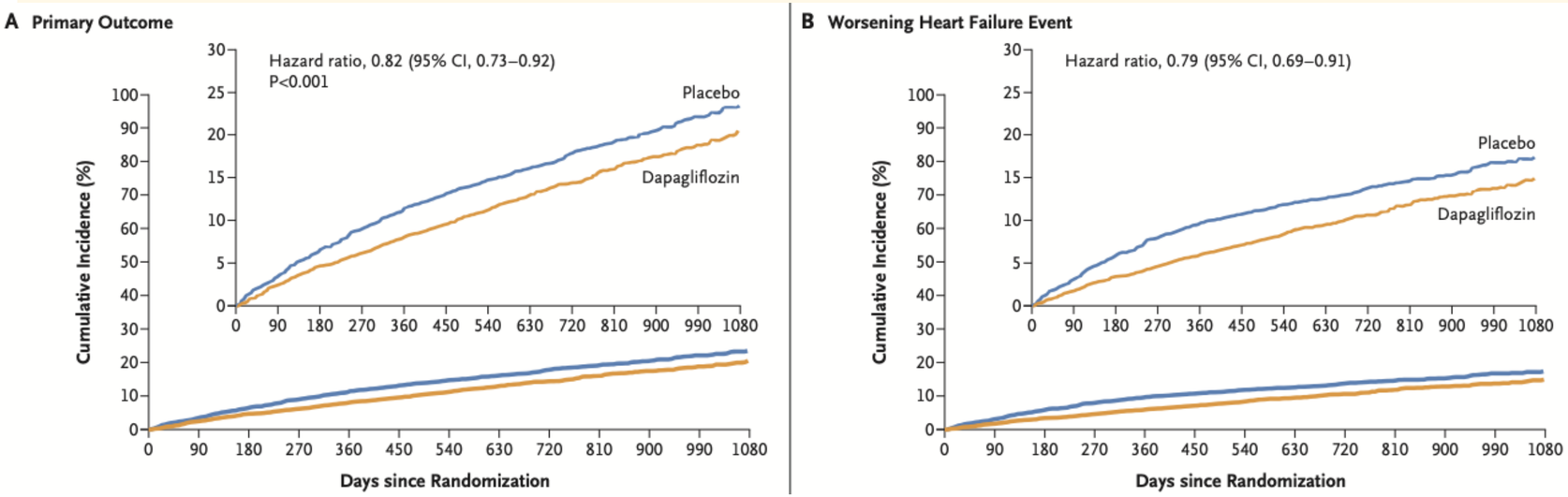
Sin diferencias en los distintos subgrupos (por FEVI, clase funcional, niveles de proBNP, FG basal, etc…

Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Sin diferencias en mortalidad

Variable	Dapagliflozin (N=3131) values	Dapagliflozin (N=3131) events/ 100 patient-yr	Placebo (N=3132) values	Placebo (N=3132) events/ 100 patient-yr	Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths†	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8¶	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA

Resultados simialres a los presentados con Empaglifozina (Emperor-Preserved)



LIMITACIONES

Menos del 5% de pacientes de raza negra

La pandemia… dificultad para evaluar síntomas en ese contexto

RESULTADOS

Sin diferencias en los distintos subgrupos (por FEVI, clase funcional, niveles de proBNP, FG basal, etc…

Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Sin diferencias en mortalidad

Variable	Dapagliflozin (N=3131) values	Dapagliflozin (N=3131) events/ 100 patient-yr	Placebo (N=3132) values	Placebo (N=3132) events/ 100 patient-yr	Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
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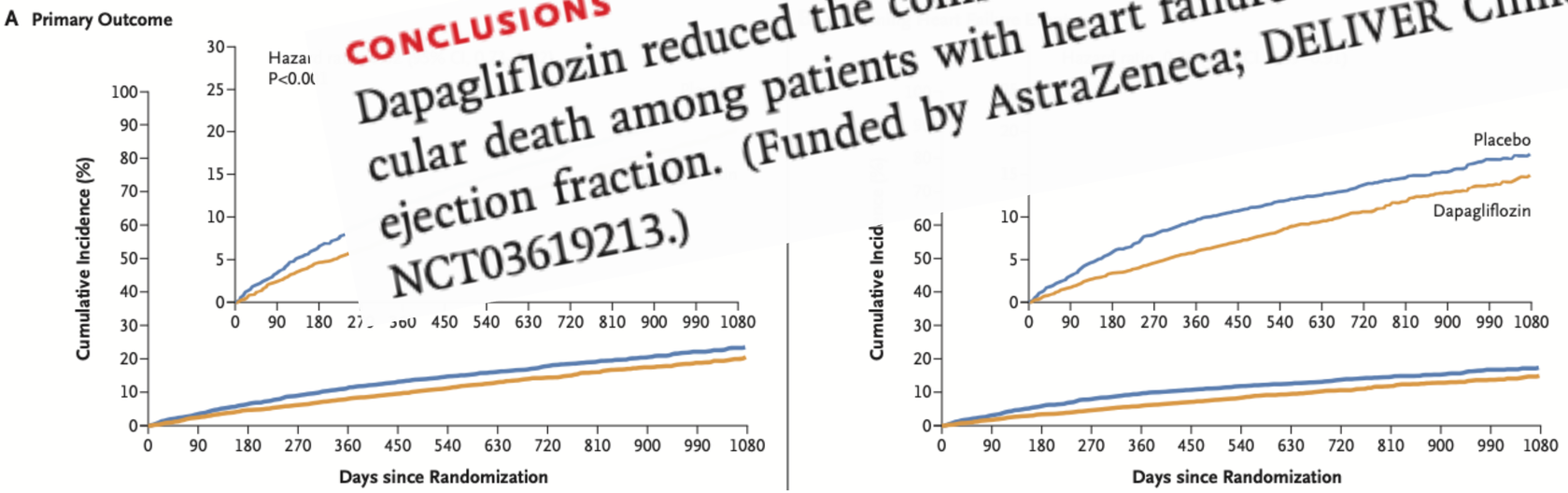
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55 [illegible]	[illegible]
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	[illegible]	[illegible]
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths†	815	11.9	[illegible]	[illegible]	[illegible]	[illegible]
Change in KCCQ total symptom score at mo 8¶	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mean change in KCCQ total symptom score at mo 8 among [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Resultados [illegible] presentados con [illegible]or-Preserved)

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)

[illegible]s
[illegible] de raza negra
[illegible] para evaluar síntomas en ese contexto



Rivaroxaban in rheumatic heart disease-associated atrial fibrillation

Connoly SJ, et al. New Engl J Med 2022. **DOI: 10.1056/NEJMoa2209051**

No se recomienda el uso de ACOD en las guías clínicas en pacientes con valvulopatía reumática… datos clínicos escasos

PACIENTES Y MÉTODOS

Criterios de inclusión: pacientes con valvulopatía reumática evidenciada por ETT y un criterio de los siguientes:

- EM moderada/severa (área de la válvula < 2 cm2)
- CHA2DS2VASC de 2 o más puntos
- Evidencia de trombo en aurícula izquierda

Randomización 1:1. Rivaroxaban (20 o 15 mg según FG) vs AVK.

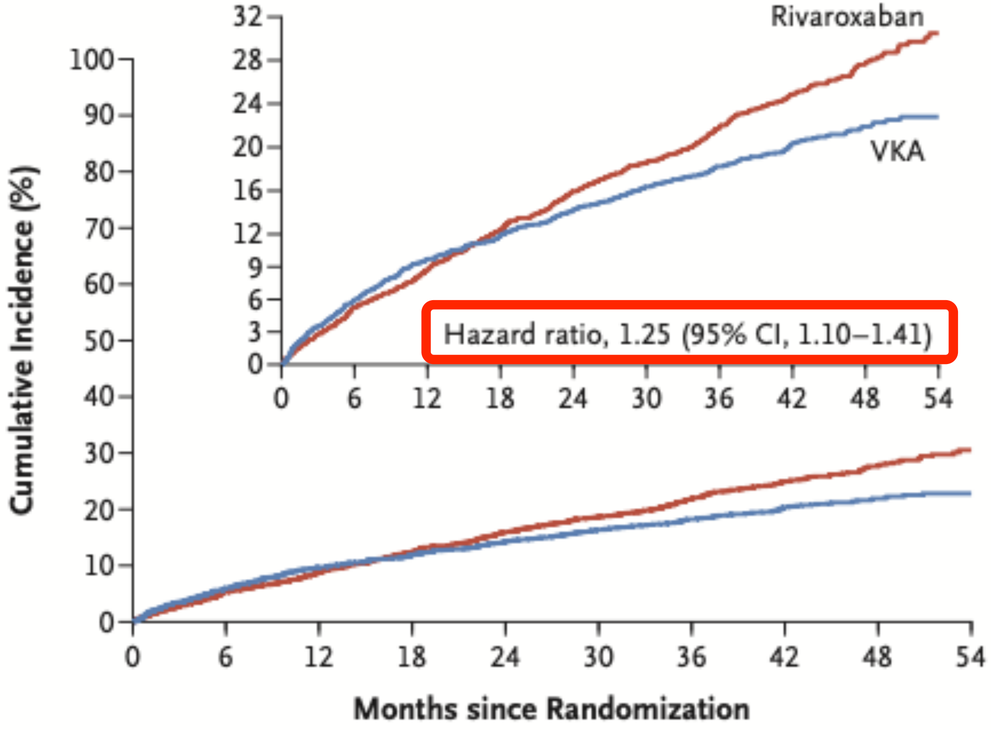
Criterios de exclusión: FG<15 ml/min y uso de otros antiagregantes en los 6 meses previos.

Endpoint primario: compuesto de ictus o embolismo sistémico. Se cambia por pocos eventos a un compuesto de ictus, embolismo, IAM o mortalidad cardiovascular

RESULTADOS

4565 incluidos entre 2016-2019. Edad media 50 años y 72.3% mujeres. Duración media del seguimiento 3.2 años. Procedencia: África, Asia y América Latina.

AVK más usado en el estudio: Warfarina (>80% pacientes). En rango terapeútico durante seguimiento en el 65% de pacientes.



No. at Risk

Rivaroxaban	2275	2124	2023	1931	1838	1750	1356	876	451	144
VKA	2256	2100	2003	1944	1880	1809	1392	881	462	138

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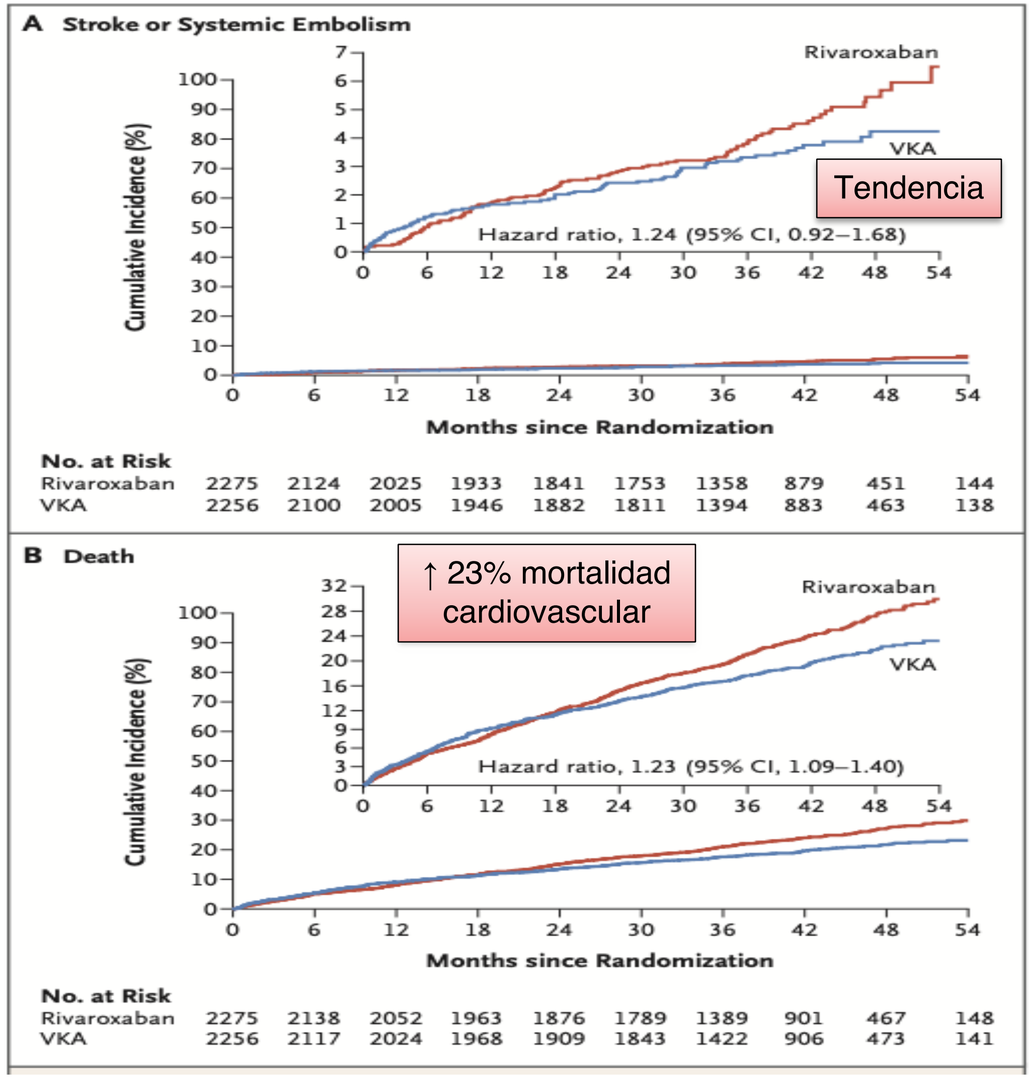
RESULTADOS

Table 2. Intention-to-Treat Analysis of Efficacy Outcomes.*

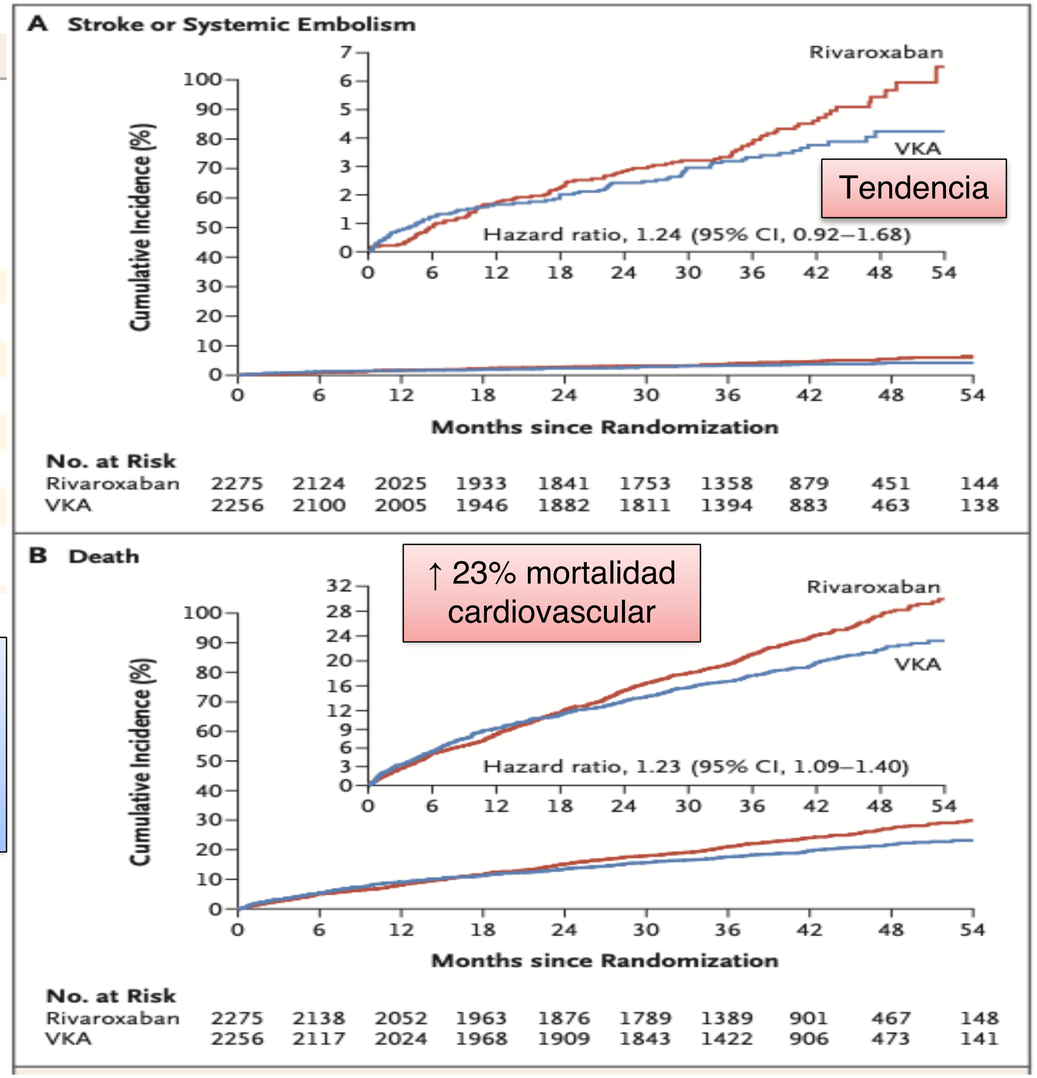
Outcome	Rivaroxaban (N=2275)			Vitamin K Antagonist (N=2256)			Proportional-Hazards Ratio (95% CI)	Difference in RMST (95% CI)	P Value
	No. of Patients	Rate	RMST	No. of Patients	Rate	RMST			
		%/yr	days		%/yr	days		days	
Stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes	560	8.21	1599	446	6.49	1675	1.25 (1.10 to 1.41)	−76 (−121 to −31)	<0.001
Stroke	90	1.32	1929	65	0.94	1950	1.37 (1.00 to 1.89)	−21 (−40 to −2)	
Ischemic stroke	74	1.08	1941	48	0.70	1963	1.53 (1.06 to 2.20)	−23 (−40 to −6)	
Hemorrhagic stroke	7	0.10	1995	7	0.10	1994	1.00 (0.35 to 2.86)	0.3 (−6 to 6)	
Stroke of uncertain cause	12	0.17	1991	10	0.14	1993	1.21 (0.52 to 2.79)	−1 (−8 to 5)	
Systemic embolism	6	0.09	1995	10	0.14	1992	0.59 (0.22 to 1.63)	4 (−3 to 10)	
Stroke or systemic embolism	94	1.38	1926	75	1.09	1942	1.24 (0.92 to 1.68)	−16 (−36 to 4)	
Myocardial infarction	5	0.07	1996	3	0.04	1998	1.67 (0.40 to 6.97)	−1 (−5 to 3)	
Death	552	7.95	1608	442	6.35	1680	1.23 (1.09 to 1.40)	−72 (−117 to −28)	
Death due to vascular causes†	439	6.33	1683	337	4.84	1751	1.29 (1.12 to 1.49)	−68 (−110 to −26)	
Sudden cardiac death	141	2.03	1894	94	1.35	1929	1.51 (1.16 to 1.96)	−36 (−58 to −13)	
Death due to mechanical or pump failure	237	3.42	1817	174	2.50	1862	1.35 (1.11 to 1.64)	−45 (−83 to −8)	
Death due to nonvascular causes	46	0.66	1962	36	0.52	1971	1.26 (0.81 to 1.94)	−9 (−25 to 7)	
Death due to unknown cause	67	0.97	1941	69	0.99	1946	0.96 (0.69 to 1.35)	−4 (−26 to 17)	
Any hospitalization	687	11.71	1432	622	10.44	1467	1.08 (0.97 to 1.21)	−36 (−80 to 9)	
Hospitalization for heart failure	240	3.61	1779	219	3.28	1794	1.08 (0.89 to 1.29)	−16 (−47 to 16)	
Valve surgery	187	2.85	1852	157	2.36	1873	1.19 (0.97 to 1.48)	−21 (−50 to 9)	
Valve surgery or valvuloplasty	205	3.14	1838	175	2.65	1859	1.17 (0.95 to 1.43)	−21 (−52 to 10)	



RESULTADOS

Table 3. On-Treatment Analysis of Safety Outcomes and Selected Efficacy Outcomes.*

Outcome	Rivaroxaban (N=2265)			Vitamin K Antagonist (N=2251)			Proportional-Hazards Ratio (95% CI)	Difference in RMST (95% CI)	P Value
	No. of Patients	Rate %/yr	RMST days	No. of Patients	Rate %/yr	RMST days		days	
Safety outcomes									
Major bleeding	40	0.67	1965	56	0.83	1954	0.76 (0.51 to 1.15)	11 (−5 to 28)	0.18
Fatal bleeding	4	0.07	1996	15	0.22	1988	0.29 (0.10 to 0.88)	8 (1 to 16)	
Bleeding in a critical area or organ	2	0.03	1998	4	0.06	1997	0.52 (0.09 to 2.81)	2 (−3 to 6)	
Intracranial hemorrhage	8	0.13	1993	14	0.21	1989	0.63 (0.26 to 1.50)	4 (−3 to 12)	
Life-threatening bleeding	22	0.36	1981	31	0.46	1975	0.77 (0.44 to 1.32)	6 (−6 to 18)	
Clinically relevant nonmajor bleeding	65	1.09	1943	71	1.06	1942	0.96 (0.68 to 1.34)	1 (−18 to 20)	
Major or clinically relevant nonmajor bleeding	102	1.72	1912	120	1.81	1901	0.89 (0.68 to 1.16)	10 (−14 to 35)	



¿POR QUÉ LA MORTALIDAD ES MAYOR CON RIVAROXABAN?

Menor adherencia al tratamiento con Rivaroxaban (¿?)

Beneficio a partir de los 3 años

- Efecto ”diferido” por mejor ajuste de INR en seguimiento (59% 1º año a 64% → 64% el 3º año)
- Estudio WARCEF: cambio de AAS a AVK con efecto “ligero” sobre la mortalidad al 4º año.

CONCLUSIONS

Among patients with rheumatic heart disease–associated atrial fibrillation, vitamin K antagonist therapy led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding. (Funded by Bayer; INVICTUS ClinicalTrials.gov number, NCT02832544.)