SESIÓN BIBLIOGRÁFICA

MEDICINA INTERNA

Noelia Carracedo Falagán
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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2023 VOL. 388 NO. 10

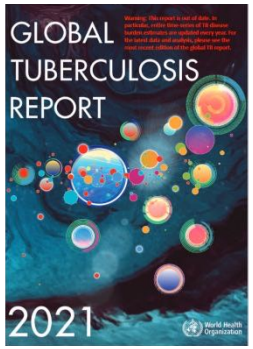
Treatment Strategy for Rifampin-Susceptible Tuberculosis

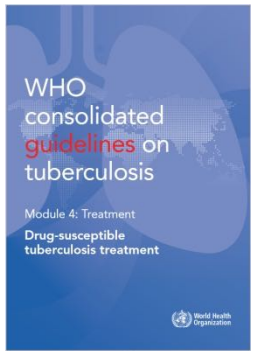
Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

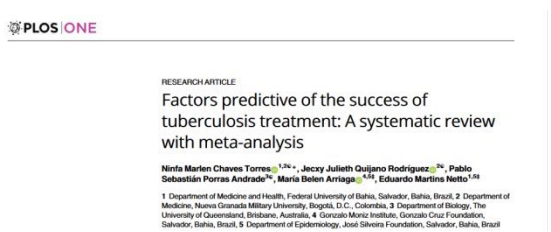
INTRODUCCIÓN

- Tratamiento estandarizado a nivel mundial en últimos 40 años TBC sensible a rifampicina **2HR + 4 HRP(E).**
  - Curación 95% en ensayos.

- Falta adherencia y limitación recursos económicos
  DURACIÓN PROLONGADA






PLOS ONE

RESEARCH ARTICLE

Factors predictive of the success of tuberculosis treatment: A systematic review with meta-analysis

Ninfa Marlen Chaves Torres[1,2*], Jecxy Julieth Quijano Rodriguez[2], Pablo Sebastián Porras Andrade[3], María Belen Arriaga[4,5], Eduardo Martins Netto[1,5]

1 Department of Medicine and Health, Federal University of Bahia, Salvador, Bahia, Brazil, 2 Department of Medicine, Nueva Granada Military University, Bogotá, D.C., Colombia, 3 Department of Biology, The University of Queensland, Brisbane, Australia, 4 Gonzalo Moniz Institute, Gonzalo Cruz Foundation, Salvador, Bahia, Brazil, 5 Department of Epidemiology, José Silveira Foundation, Salvador, Bahia, Brazil

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Int J Infect Dis. 2021 December ; 113(Suppl 1): S7–S12. doi:10.1016/j.ijid.2021.02.107.

Global Tuberculosis Report 2020 – Reflections on the Global TB burden, treatment and prevention efforts

Jeremiah Chakaya[a,b,*], Mishal Khan[c], Francine Ntoumi[e,f], Eleni Aklillu[g], Razia Fatima[d], Peter Mwaba[h], Nathan Kapata[i], Sayoki Mfinanga[j,k,l], Seyed Ehtesham Hasnain[m], Patrick D.M.C. Katoto[n], André N.H. Bulabula[o], Nadia A. Sam-Agudu[p,q,r], Jean B. Nachega[s,t,u], Simon Tiberi[v,w], Timothy D. McHugh[x], Ibrahim Abubakar[y], Alimuddin Zumla[z]

- Incumplimiento terapético
- Generación de RESISTENCIAS

No se cumplen objetivos
ERRADICACIÓN
a nivel MUNDIAL

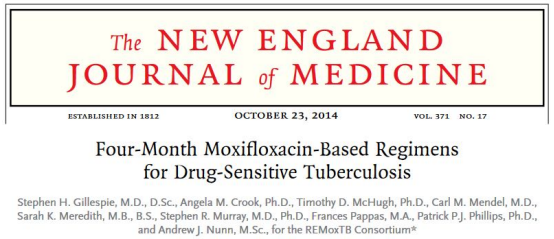
Junta de Castilla y León Consejería de Sanidad · Sacyl · Complejo Asistencial Universitario de León

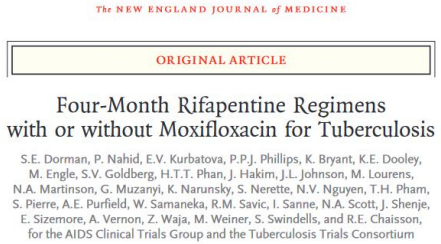
INTRODUCCIÓN

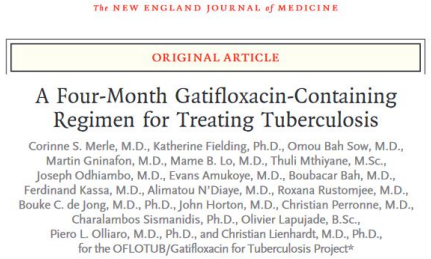
- Ensayos publicados ⇨ TASAS CURACIÓN 85%
  - Con regímenes 3-4 meses ⇨ MAYOR si incluye QUINOLONA/RIFAPENTINA.
  - Regímenes de 2 meses con baciloscopia negativa.

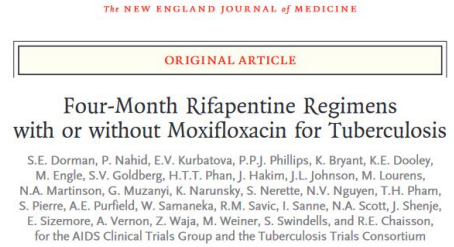
✓ SOBRETRATAMIENTO mayoria para PREVENIR RECAIDAS en una minoria.


Cochrane Library
Cochrane Database of Systematic Reviews
Regimens of less than six months for treating tuberculosis (Review)
Gelband H


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17
Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis
Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis
Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Marne B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*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- Tratamiento inicial de 8 semanas:
  - Ampliación en enfermedad clínica persistente.
  - Seguimiento posterior a tratamiento.
  - Retratamiento precoz para minoria casos: recaida.

✓ No inferior tratamiento estandar.

✓ Duración menor.

MÉTODOS

DISEÑO DEL ESTUDIO

- **TRUNCATE-TB:** Two-Month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-Sensitive Tuberculosis.

- **Ensayo en fase 2-3**
  - Prospectivo, multicéntrico, internacional, adaptativo, multi-grupo, multi-etapas, aleatorizado, abierto, de no inferioridad.
  - Periodo de seguimiento de 96 semanas.

- 18 centros.

NUS National University of Singapore

Junta de Castilla y León
Consejería de Sanidad

Sacyl

Complejo Asistencial Universitario de León

CRITERIOS DE INCLUSIÓN	CRITERIOS EXCLUSIÓN
✓ Edad: 18 a 65 años.	✓ Tuberculostáticos o quinolonas 3 meses previos.
✓ Clínica compatible y/o evidencia Rx tórax	✓ Enfemedad tuberculosa previa tratada (no excluída quimioprofilaxis infección TBC).
✓ PCR positiva esputo (GeneXpert) S a R.	✓ TBC extrapulmonar (no excluyente derrame pleural <50% o adenopatías intra/extratorácicas).
✓ Disposición cumplir visitas/seguimiento.	✓ Formas graves con insuficiencia respiratoria y/o que requieran ingreso.
✓ Residencia fija y mantenida durante periodo seguimiento estudio.	✓ **Baciloscopia 3 + (WHO/IUATLD).** *
✓ Disposición terapia observada.	✓**Caverna > 4 cm en Rx.** *
✓ Consentimiento informado.	✓ DM mal controlada.
	✓ Neoplasia en tratamiento QT/RT activo.
	✓ Antecedentes IAM, IC, arrítmias o cardiopatías congénitas.
	✓ EPOC severo (MRC >/ 3).
	✓ **Crisis comiciales.** *
	✓ **Tendinopatía asociada a quinolonas.** *
	✓ Neuropatia periférica sintomática.
	✓ Consumo alcohol/drogas.
	✓ Embarazo o lactancia.
	✓ Tratamiento concomitante prolongue QT o interacciones con F .
	✓ Tratamiento inmunosupresor o esteroides en los 2 meses previos.
	✓ Alteración visión cromática.
	✓ QT > 450 mseg o alteraciones ECG compatibles con isquemia y/o arritmias.
	✓ Laboratorio: N< 1000, Hb <7, Plaq < 50.000, CCr < 60, AST > 3 veces, K < 3.5.
	✓ **VIH** * (excepto: CD4 > 200, no TARGA actual, diferir inicio TAR hasta semana 8 tras inicio o 12 si se aleatoriza a regimen potenciado).

MÉTODOS

POBLACIÓN

Quantified result	Interpretation ATS scale (threshold at 1/100 fields)	Interpretation WHO scale (threshold at 4/100 fields)	Interpretation IUATLD scale (threshold at 1/10 fields)
Negative	Negative	Negative	Negative
1–2 AFB per 300 fields	Doubtful	Doubtful negative	Doubtful
1–3 AFB per 100 fields	Positive 1+	Doubtful negative	Doubtful
4–9 AFB per 100 fields	Positive 1+	Doubtful positive	Doubtful
1–9 AFB per 10 fields	Positive 2+	Positive 1+	Positive 1+
1–9 AFB per field	Positive 3+	Positive 2+	Positive 2+
10 or more AFB per field	Positive 4+	Positive 3+	Positive 3+

ATS = American Thoracic Society; WHO = World Health Organization; IUATLD = International Union Against Tuberculosis and Lung Disease.

Quantification scales and thresholds

CRITERIOS DE INCLUSIÓN	CRITERIOS EXCLUSIÓN
✓ Edad: 18 a 65 años.	✓ Tuberculostáticos o quinolonas 3 meses previos.
✓ Clínica compatible y/o evidencia Rx tórax	✓ Enfemedad tuberculosa previa tratada (no excluída quimioprofilaxis infección TBC).
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✓ Disposición cumplir visitas/seguimiento.	✓ Formas graves con insuficiencia respiratoria y/o que requieran ingreso.
✓ Residencia fija y mantenida durante periodo seguimiento estudio.	✓ **Baciloscopia 3 + (WHO/IUATLD).** *
✓ Disposición terapia observada.	✓**Caverna > 4 cm en Rx.** *
✓ Consentimiento informado.	✓ DM mal controlada.
	✓ Neoplasia en tratamiento QT/RT activo.
	✓ Antecedentes IAM, IC, arrítmias o cardiopatías congénitas.
	✓ EPOC severo (MRC >/ 3).
	✓ **Crisis comiciales.** *
	✓ **Tendinopatía asociada a quinolonas.** *
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	✓ Consumo alcohol/drogas.
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	✓ Tratamiento concomitante prolongue QT o interacciones con F .
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	✓ Alteración visión cromática.
	✓ QT > 450 mseg o alteraciones ECG compatibles con isquemia y/o arritmias.
	✓ Laboratorio: N< 1000, Hb <7, Plaq < 50.000, CCr < 60, AST > 3 veces, K < 3.5.
	✓ **VIH** * (excepto: CD4 > 200, no TARGA actual, diferir inicio TAR hasta semana 8 tras inicio o 12 si se aleatoriza a regimen potenciado).

MÉTODOS

ALEATORIZACIÓN

RIESGO RECAIDA

LUGAR PROCEDENCIA

Defining the Optimal Dose of Rifapentine for Pulmonary Tuberculosis: Exposure–Response Relations From Two Phase II Clinical Trials

RM Savic[1], M Weiner[2,3], WR MacKenzie[4], M Engle[3], WC Whitworth[4], JL Johnson[5,6], P Nsubuga[6], P Nahid[7,8], NV Nguyen[8], CA Peloquin[9], KE Dooley[10], SE Dorman[10]
for the Tuberculosis Trials Consortium of the Centers for Disease Control and Prevention

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 102 NUMBER 2 | AUGUST 2017

- Baciloscopia negativa.
- Caverna /< 4 cm.
- VIH negativo.

BAJO RIESGO

- Baciloscopia positiva.
- Carverna /< 4 cm.
- VIH negativo.

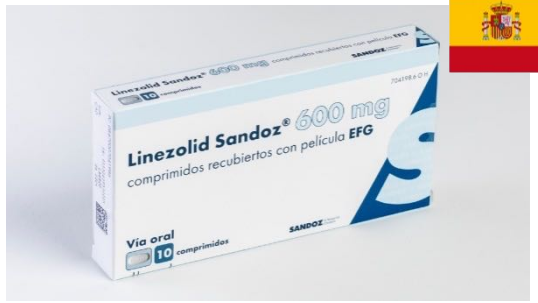
RIESGO INTERMEDIO

- Baciloscopia positiva (+3).
- Caverna > 4 cm.
- VIH positivo.

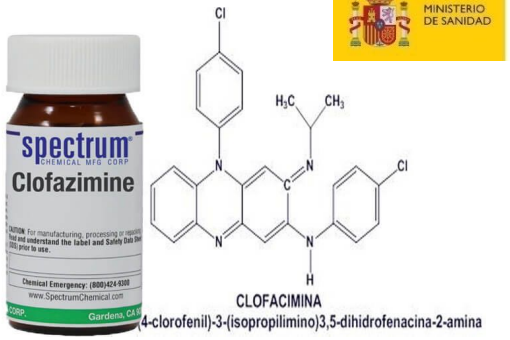
ALTO RIESGO

MÉTODOS

ESTRATEGIA DE TRATAMIENTO



- ***M. tuberculosis.***
- Micobacterias no tuberculosas crecimiento lento:
  - *M. marinum, M. ulcerans, M kansasii.*
- Escasa actividad frente a MAC y micobacterias de escaso crecimiento.



- *La mayoría cepas **M. tuberculosis**, M. avium-complex, M. kansasii, M szulgai, M simiae, M. malmoense, M. haemophilum, M xenopi.*
- Mayoria de *M. abscessus* y *M. chelonae* y cerca 50% *M. fortuitum* son resistentes.
- <u>Resistencia cruzada con bedaquilina frente a M. tuberculosis</u> (bomba que puede extraer ambos fármacos).

- ***M. tuberculosis complex**: M. tuberculosis, M. bovis y M. africanum;* con CMI 2-4 veces menor que la rifampicina (resistencia cruzada con rifampicina).
- *M. avium complex, M. kansasii y M. leprae.*

- ***M. tuberculosis**, M. bovis, M. avium intracelulares, M. kansasii, M. ulcerans, M. frtiutim, M. chelonae, M abscessus y M. leprae.*
- No actividad: *M. xenopi y M. novocastrense.*

- ***M. tuberculosis** , M. kansasii y M. fortiutum.*
- Suelen ser resistentes*: M. avium intracellulare, M. chelonae y M. abscessus.*

MÉTODOS

ESTRATEGIA DE TRATAMIENTO

A. Standard treatment arm

For first 8 weeks

DRUG	<40KG	40-54 KG	55-70KG	≥71KG
Rifampicin	300mg	450mg	600mg	750mg
Isoniazid	150mg	225mg	300mg	375mg
Pyrazinamide	800mg	1200mg	1600mg	2000mg
Ethambutol	550mg	825mg	1100mg	1375mg

For subsequent weeks to week 24

DRUG	<40KG	40-54 KG	55-70KG	≥71KG
Rifampicin	300mg	450mg	600mg	750mg
Isoniazid	150mg	225mg	300mg	375mg

B. Rifampicin-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Rifampicin	35mg/kg (rounded to nearest 150mg, maximum 2100mg)*			
Isoniazid	150mg	225mg	300mg	375mg
Pyrazinamide	800mg	1200mg	1600mg	2000mg
Ethambutol	550mg	825mg	1100mg	1375mg
Linezolid	600mg			

*The dose of rifampicin was decreased from 35mg/kg to 20mg/kg for all participants from 1st November 2019 after 88 participants had been enrolled in this arm (recommendation of the Trial Steering Committee as a precaution following a death from drug-induced liver injury in this arm).

C. Rifampicin-clofazimine arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Rifampicin	35mg/kg (rounded to nearest 150mg, maximum 2100mg)			
Isoniazid	150mg	225mg	300mg	375mg
Pyrazinamide	800mg	1200mg	1600mg	2000mg
Ethambutol	550mg	825mg	1100mg	1375mg
Clofazimine	200mg			

D. Rifapentine-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Isoniazid	5mg/kg rounded to nearest 100mg		300mg	
Pyrazinamide	25mg/kg rounded to nearest 500mg	1000mg	1500mg	2000mg
Rifapentine	1200mg			
Linezolid	600mg			
Levofloxacin	1000mg			

E. Bedaquiline-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Bedaquiline	400 mg once daily for 2 weeks then 200mg three times a week			
Isoniazid	5mg/kg rounded to nearest 100mg		300mg	
Pyrazinamide	25mg/kg rounded to nearest 500mg	1000mg	1500mg	2000mg
Ethambutol	15mg/kg (rounded to nearest 100mg, maximum 1600mg)			
Linezolid	600mg			

MÉTODOS

ESTRATEGIA DE TRATAMIENTO

Tratamiento acortado se AMPLIABA a 12 semanas

- Enfermedad clínica persistente: síntomas y cultivo esputo positivo.
- Incumplimiento terapéutico.

CAMBIO PAUTA ESTÁNDAR 24 semanas

- Enfermedad clínica persistente semana 12.
- Efectos adversos "precoces".
- Criterios recaída (clínica, Rx, cultivo esputo + finalizar tto y 4 sem post-tto).

- Supervisión diaria hasta cumplir 8 semanas de tratamiento para todos regímenes.

MÉTODOS

ESTRATEGIA DE TRATAMIENTO

- **Comité de análisis de datos** ⇨ 2 análisis intermedios valorar interrupción del reclutamiento:
  - Tasa fracaso terapéutico/recaída > 25% y tasa tiempo conversión cultivo (HR < 0.8).
  - CONCLUSIÓN: **NO interrupción** RECLUTAMIENTO.
- **Comité Directivo** a interrupción reclutamiento "precoz" de 2 grupos
  - **Rifapentina-Linezolid** (tras 42 pac) ⇨ nº comprimidos (15 vs 9-10) y toxicidad quinolonas.
  - **Clofazimina** (tras 78 pac) ⇨ restricciones licencias importación.

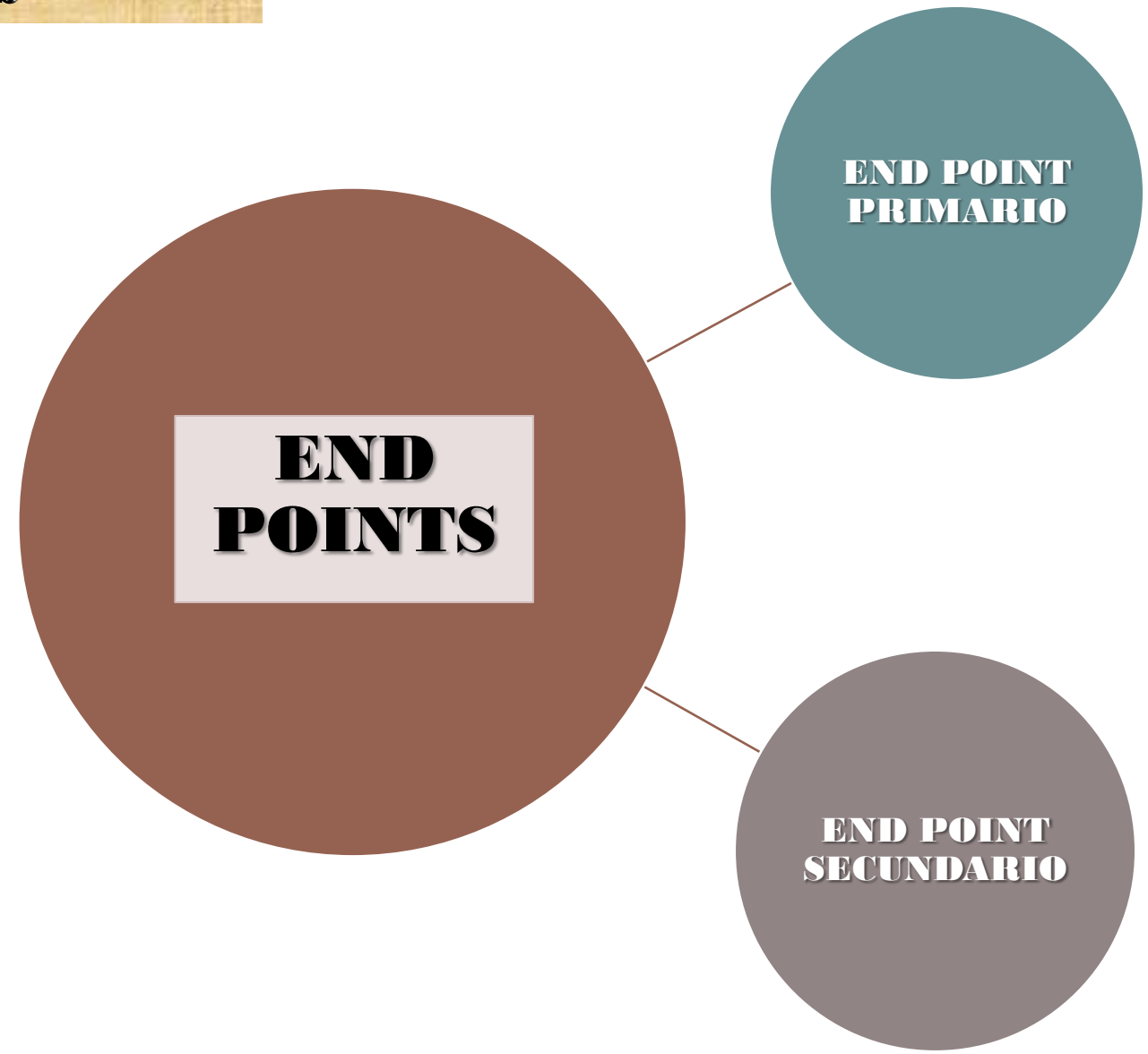
MÉTODOS

EVALUACIONES Y RESULTADOS

- Seguimiento clinico:
  - 1, 2, cada 2 semanas hasta 24 semana; posteriormente cada 12 semanas hasta 96 semana.
  - A partir 30 sem intercalaban presenciales con telefónicas.
  - Cada visita:
    - Checklist síntomas.
    - Efectos adversos.
    - Adherencia terapéutica
  - Rx tórax: inicio, semana 8 y 96 (fin), sospecha recaída.
  - Evaluación DISNEA:
    - Escala MRC: >/ 3.
    - Espirometria: FEV1 < 50%.
  - Esputo: tinción y cultivo (cada visita) y si riesgo recaída.
  - Resistencias al inicio y en recaídas.
  - PCR *M. tuberculosis* ⇨ inicio y recaída.
  - Cuestionario en 48 y 96 semanas.

MÉTODOS

OBJETIVOS



- COMPUESTO: RESULTADOS CLÍNICOS INSATISFACTORIOS EN 96 SEM
  - Muerte previa 96 semana.
  - Tuberculosis activa 96 semana.
  - Requerir tratamiento hasta 96 semana.

- Tiempo total de tratamiento.
- Efectos adversos grado 3-4.
- Resistencia farmacológica adquirida.

RESULTADOS

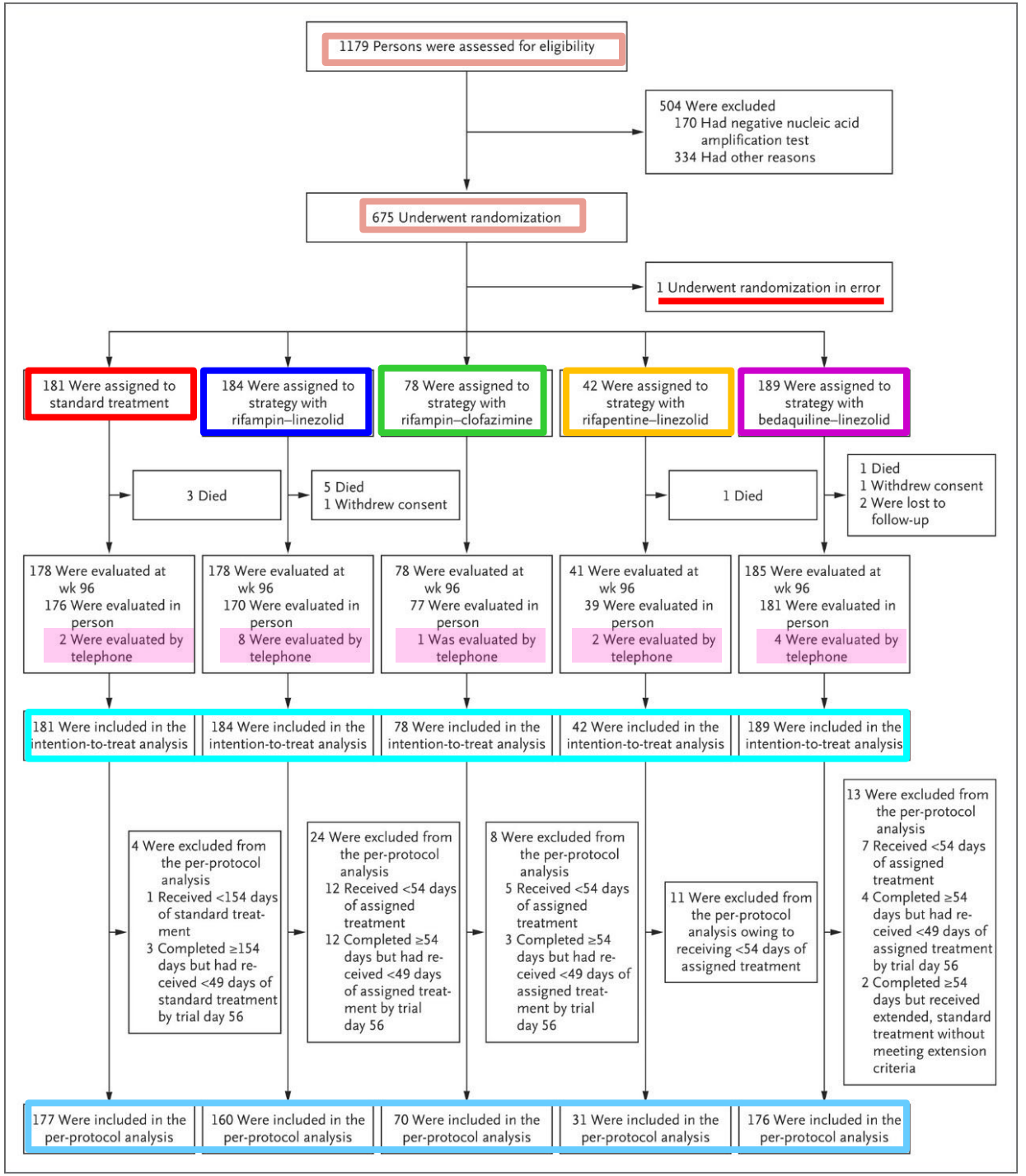
- 21 marzo 2018 a 20 marzo 2020.

- Grupo tratamiento estándar:
  - 98% completaron tratamiento.
  - 3.3% re-tratamiento.
- 4 grupos comparativos:
  - 91.5% (rango 73.8 a 94.7) tto 8 semanas.
  - 6.5 % cambio a tratamiento estándar 24 sem (eventos adversos).
  - 17% global (rango 12.7 a 22.8) se someten a una nueva pauta tratamiento.

- 17 pac (2.6%).

N= 674.

N= 614.



RESULTADOS

Table 1. Baseline Characteristics of the Participants in the Intention-to-Treat Population.*

Characteristic	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Clofazimine (N=78)†	Strategy with Rifapentine–Linezolid (N=42)†	Strategy with Bedaquiline–Linezolid (N=189)	Overall (N=674)
Male sex — no. (%)	119 (66)	113 (61)	48 (62)	25 (60)	116 (61)	421 (62)
Age group — no. (%)						
18–34 yr	104 (57)	109 (59)	51 (65)	26 (62)	95 (50)	385 (57)
35–50 yr	59 (33)	57 (31)	21 (27)	11 (26)	70 (37)	218 (32)
51–65 yr	18 (10)	18 (10)	6 (8)	5 (12)	24 (13)	71 (11)
Country — no. (%)						
Indonesia	78 (43)	73 (40)	38 (49)	23 (55)	82 (43)	294 (44)
Philippines	61 (34)	66 (36)	32 (41)	15 (36)	63 (33)	237 (35)
Thailand	10 (6)	15 (8)	8 (10)	4 (10)	12 (6)	49 (7)
Uganda	28 (15)	25 (14)	0	0	27 (14)	80 (12)
India	4 (2)	5 (3)	0	0	5 (3)	14 (2)
Median body weight (range) — kg	50 (32–81)	50 (30–97)	48 (35–88)	50 (32–71)	50 (32–86)	50 (30–97)
Median body-mass index (range)‡	19 (14–29)	19 (14–33)	19 (14–29)	18 (12–25)	19 (13–30)	19 (12–33)
Body-mass index — no. (%)‡						
<17	39 (22)	42 (23)	21 (27)	13 (31)	47 (25)	162 (24)
17 to <18.5	40 (22)	38 (21)	14 (18)	9 (21)	29 (15)	130 (19)
≥18.5	102 (56)	104 (57)	43 (55)	20 (48)	113 (60)	382 (57)
Employment status — no. (%)						
Working full or part time	94 (52)	99 (54)	35 (45)	16 (38)	100 (53)	344 (51)
Student	10 (6)	15 (8)	10 (13)	10 (24)	15 (8)	60 (9)
Not working	77 (43)	70 (38)	33 (42)	16 (38)	74 (39)	270 (40)
Current smoker — no. (%)	34 (19)	33 (18)	15 (19)	8 (19)	31 (16)	121 (18)
Former smoker — no. (%)	58 (32)	63 (34)	24 (31)	13 (31)	51 (27)	209 (31)
Proportion of lung affected on chest radiograph — no. (%)						
<25%	46 (25)	62 (34)	28 (36)	12 (29)	53 (28)	201 (30)
25–50%	94 (52)	87 (47)	36 (46)	24 (57)	98 (52)	339 (50)
>50%	41 (23)	35 (19)	14 (18)	6 (14)	38 (20)	134 (20)
Cavitation on chest radiograph — no. (%)						
Absent	87 (48)	83 (45)	41 (53)	19 (45)	81 (43)	311 (46)
Largest cavity ≤4 cm	90 (50)	96 (52)	37 (47)	23 (55)	106 (56)	352 (52)
Largest cavity >4 cm	4 (2)	5 (3)	0	0	2 (1)	11 (2)
WHO smear grade — no./total no. (%)§						
Negative	46/180 (26)	57/184 (31)	26/78 (33)	12/41 (29)	50/189 (26)	191/672 (28)
Scanty	27/180 (15)	28/184 (15)	12/78 (15)	7/41 (17)	24/189 (13)	98/672 (15)
1+	38/180 (21)	48/184 (26)	25/78 (32)	13/41 (32)	53/189 (28)	177/672 (26)
2+	44/180 (24)	37/184 (20)	8/78 (10)	7/41 (17)	38/189 (20)	134/672 (20)
3+	25/180 (14)	14/184 (8)	7 /78 (9)	2/41 (5)	24/189 (13)	72/672 (11)
Bacillary burden on nucleic acid amplification test — no./total no. (%)¶						
Very low	25/173 (14)	22/172 (13)	8/74 (11)	3/37 (8)	16/184 (9)	74/642 (12)
Low	40/173 (23)	48/172 (28)	22/74 (30)	11/37 (30)	52/184 (28)	173/642 (27)
Medium	72/173 (42)	80/172 (47)	31/74 (42)	15/37 (41)	73/184 (40)	271/642 (42)
High	36/173 (21)	22/172 (13)	13/74 (18)	8/37 (22)	43/184 (23)	122/642 (19)
Positive sputum culture — no. (%)	166 (92)	168 (91)	68 (87)	39 (93)	171 (90)	612 (91)
Drug resistance — no./total no. (%)						
Isoniazid	12/162 (7)	15/166 (9)	5/68 (7)	2/39 (5)	12/169 (7)	46/604 (8)
Pyrazinamide	5/133 (4)	2/135 (1)	5/54 (9)	1/29 (3)	5/136 (4)	18/487 (4)
Ethambutol	1/162 (1)	0	2/68 (3)	0	2/169 (1)	5/604 (1)
Relapse risk — no. (%)**						
Low	47 (26)	57 (31)	26 (33)	13 (31)	50 (26)	193 (29)
Intermediate	105 (58)	111 (60)	45 (58)	27 (64)	113 (60)	401 (59)
High	29 (16)	16 (9)	7 (9)	2 (5)	26 (14)	80 (12)

RESULTADOS

OBJETIVO PRIMARIO

- Grupo rifampicina-linezolid: 11.4%
  - Tasa ajustada: 7.4 puntos porcentuales; IC 97.5%: 1.7 a 13.2.
  - Criterio de no inferioridad NO CUMPLIDO.
- Grupo bedaquilina-linezolid: 5.8%
  - Tasa ajustada: 0.8 puntos porcentuales; IC 97.5%: -3.4 a 5.1.
  - Criterio de no inferioridad CUMPLIDO.

Table 2. Primary Efficacy Outcome.*

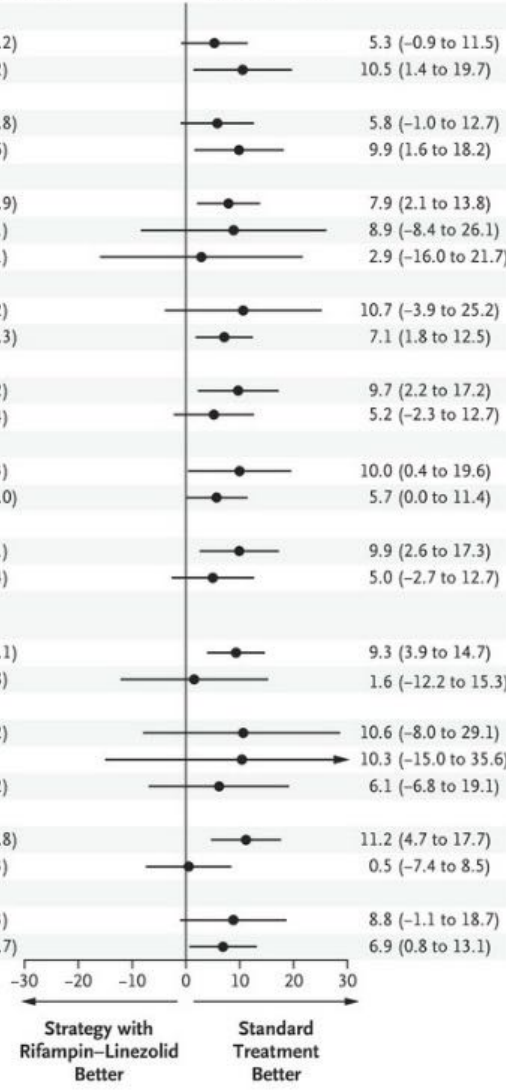
Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment
			Adjusted Difference (97.5% CI)†		Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (−3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease‖	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (−3.4 to 5.1)
Per-protocol population‡‡					
Primary outcome — no./total no. (%)	6/177 (3.4)	17/160 (10.6)	6.9 (0.9 to 12.8)	9/176 (5.1)	0.9 (−3.3 to 5.1)

RESULTADOS

OBJETIVO PRIMARIO

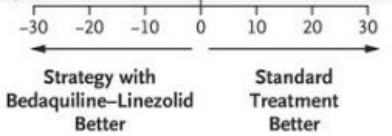
A Primary Outcome in Strategy Group with Initial Rifampin–Linezolid Regimen vs. Standard-Treatment Group

Subgroup	Strategy with Rifampin–Linezolid no. of participants with event/total no. (%)	Standard Treatment no. of participants with event/total no. (%)	Difference (95% CI) percentage points
Sex			
Male	11/113 (9.7)	5/119 (4.2)	5.3 (−0.9 to 11.5)
Female	10/71 (14.1)	2/62 (3.2)	10.5 (1.4 to 19.7)
Age			
18–34 yr	11/109 (10.1)	5/104 (4.8)	5.8 (−1.0 to 12.7)
35–65 yr	10/75 (13.3)	2/77 (2.6)	9.9 (1.6 to 18.2)
Country			
Indonesia or Philippines	15/139 (10.8)	4/139 (2.9)	7.9 (2.1 to 13.8)
Uganda	4/25 (16.0)	2/28 (7.1)	8.9 (−8.4 to 26.1)
India or Thailand	2/20 (10.0)	1/14 (7.1)	2.9 (−16.0 to 21.7)
Education			
0–7 yr	7/37 (18.9)	4/49 (8.2)	10.7 (−3.9 to 25.2)
≥8 yr	14/147 (9.5)	3/132 (2.3)	7.1 (1.8 to 12.5)
Smoking status			
Never	11/88 (12.5)	2/89 (2.2)	9.7 (2.2 to 17.2)
Current or former	10/96 (10.4)	5/92 (5.4)	5.2 (−2.3 to 12.7)
Body-mass index			
<18.5	13/80 (16.3)	5/79 (6.3)	10.0 (0.4 to 19.6)
≥18.5	8/104 (7.7)	2/102 (2.0)	5.7 (0.0 to 11.4)
Cavitation on chest radiograph			
Absent	10/83 (12.0)	1/87 (1.1)	9.9 (2.6 to 17.3)
Present	11/101 (10.9)	6/94 (6.4)	5.0 (−2.7 to 12.7)
Proportion of lung affected on chest radiograph			
≤50%	17/149 (11.4)	3/140 (2.1)	9.3 (3.9 to 14.7)
>50%	4/35 (11.4)	4/41 (9.8)	1.6 (−12.2 to 15.3)
WHO smear grade			
Negative	7/57 (12.3)	1/46 (2.2)	10.6 (−8.0 to 29.1)
Scanty or 1+	7/76 (9.2)	0/65	10.3 (−15.0 to 35.6)
2+ or 3+	7/51 (13.7)	5/69 (7.2)	6.1 (−6.8 to 19.1)
Grade on MRC breathlessness scale			
Grade 1	17/126 (13.5)	3/106 (2.8)	11.2 (4.7 to 17.7)
Grade 2 or higher	4/58 (6.9)	4/75 (5.3)	0.5 (−7.4 to 8.5)
Relapse risk			
Low	7/57 (12.3)	2/47 (4.3)	8.8 (−1.1 to 18.7)
Intermediate or high	14/127 (11.0)	5/134 (3.7)	6.9 (0.8 to 13.1)



B Primary Outcome in Strategy Group with Initial Bedaquiline–Linezolid Regimen vs. Standard-Treatment Group

Subgroup	Strategy with Bedaquiline–Linezolid no. of participants with event/total no. (%)	Standard Treatment no. of participants with event/total no. (%)	Difference (95% CI) percentage points
Sex			
Male	5/116 (4.3)	5/119 (4.2)	0.1 (−4.4 to 4.6)
Female	6/73 (8.2)	2/62 (3.2)	3.6 (−3.9 to 11.2)
Age			
18–34 yr	4/95 (4.2)	5/104 (4.8)	−1.8 (−7.0 to 3.4)
35–65 yr	7/94 (7.4)	2/77 (2.6)	4.8 (−1.1 to 10.7)
Country			
Indonesia or Philippines	6/145 (4.1)	4/139 (2.9)	1.3 (−3.0 to 5.5)
Uganda	4/27 (14.8)	2/28 (7.1)	7.7 (−8.8 to 24.1)
India or Thailand	1/17 (5.9)	1/14 (7.1)	−1.3 (−18.8 to 16.3)
Education			
0–7 yr	3/48 (6.3)	4/49 (8.2)	−2.4 (−12.1 to 7.3)
≥8 yr	8/141 (5.7)	3/132 (2.3)	2.8 (−1.6 to 7.3)
Smoking status			
Never	8/107 (7.5)	2/89 (2.2)	3.7 (−2.2 to 9.5)
Current or former	3/82 (3.7)	5/92 (5.4)	−1.0 (−7.0 to 5.0)
Body-mass index			
<18.5	4/76 (5.3)	5/79 (6.3)	−1.3 (−8.5 to 6.0)
≥18.5	7/113 (6.2)	2/102 (2)	3.3 (−2.0 to 8.6)
Cavitation on chest radiograph			
Absent	5/81 (6.2)	1/87 (1.1)	3.4 (−2.4 to 9.2)
Present	6/108 (5.6)	6/94 (6.4)	−0.6 (−7.0 to 5.9)
Proportion of lung affected on chest radiograph			
≤50%	8/151 (5.3)	3/140 (2.1)	2.8 (−1.0 to 6.6)
>50%	3/38 (7.9)	4/41 (9.8)	−2.2 (−14.4 to 10.1)
WHO smear grade			
Negative	1/50 (2.0)	1/46 (2.2)	0.9 (−16.8 to 18.7)
Scanty or 1+	4/77 (5.2)	0/65	6.4 (−18.7 to 31.6)
2+ or 3+	6/62 (9.7)	5/69 (7.2)	2.0 (−9.8 to 13.8)
Grade on MRC breathlessness scale			
Grade 1	3/112 (2.7)	3/106 (2.8)	1.1 (−3.0 to 5.2)
Grade 2 or higher	8/77 (10.4)	4/75 (5.3)	3.5 (−5.0 to 11.9)
Relapse risk			
Low	1/50 (2.0)	2/47 (4.3)	−0.8 (−7.3 to 5.6)
Intermediate or high	10/139 (7.2)	5/134 (3.7)	2.6 (−2.6 to 7.8)



Junta de Castilla y León Consejería de Sanidad · Sacyl · Complejo Asistencial Universitario de León

RESULTADOS

OBJETIVOS SECUNDARIOS

- Division of AIDS Toxicity Criteria:
  - Grado 1: leve.
  - Grado 2: moderado.
  - Grado 3: severo.
  - Grado 4: potencialmente mortal.
  - Grado 5: muerte.

- Ambos casos con R fenotípicas y genotípica a bedaquilina y clofazimina. (delección 198 mmpR5)

- 1º: resistencia resistencia a H al inicio
  - Se interrumpio tratamiento durante 14 días en las primeras 4 semanas y tuvó una recaída en la 52 sem.
- 2º: completó tratamiento 8 semanas y tuvo recaída en 36 sem.

Table 3. Secondary Outcomes.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment Difference (95% CI)†	Strategy with Bedaquiline–Linezoli (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment Difference (95% CI)†
Participant-centered outcomes					
Total treatment time through wk 96 — days‡					
Total duration of treatment	180.2±37.9	105.7±80.1	−74.5 (−87.4 to −61.6)	84.8±65.3	−95.3 (−106.2 to −84.5)
Total qualifying treatment time	177.3±35.6	101.6±74.9	−75.7 (−87.7 to −63.6)	83.8±64.2	−93.5 (−104.0 to −82.9)
Acceptability scores§					
Difficulty score	1.5±1.7	2.4±2.2	1.0 (0.6 to 1.4)	1.8±2.0	0.4 (0.0 to 0.8)
Anxiety score	3.6±2.2	3.9±2.0	0.3 (−0.1 to 0.8)	3.4±2.0	−0.2 (−0.6 to 0.3)
Motivation score	6.2±3.9	8.0±3.0	1.8 (1.1 to 2.5)	8.1±2.9	1.9 (1.2 to 2.6)
Preferred treatment recommendation to others — no. (%)					
2-Mo treatment	NA	126/176 (71.6)	—	141/180 (78.3)	—
6-Mo treatment	NA	35/176 (19.9)	—	25/180 (13.9)	—
No preference	NA	15/176 (8.5)	—	14/180 (7.8)	—
Quality-of-life scores¶					
Mental health summary score	57.5±0.5	57.5±0.5	−0.02 (−1.35 to 1.30)	57.8±0.5	0.33 (−1.02 to 1.68)
Physical health summary score	56.7±0.5	56.8±0.5	0.06 (−1.24 to 1.37)	56.7±0.5	0.00 (−1.25 to 1.26)
Health-status score‖	0.99±0.0	0.98±0.1	−0.01 (−0.02 to 0.00)	0.98±0.1	−0.01 (−0.02 to 0.01)
Body weight**					
Change from baseline — kg	5.8±4.8	5.6±4.7	−0.3 (−1.3 to 0.6)	6.1±4.8	0.2 (−0.7 to 1.2)
Change from baseline — %	11.9±10.0	11.4±9.8	−0.8 (−2.8 to 1.3)	12.1±9.8	0.3 (−1.7 to 2.4)
Safety outcomes					
Adverse events through wk 96 — no. (%)					
Any grade 3 or 4 adverse event	29 (16.0)	32 (17.4)	1.4 (−6.4 to 9.2)	30 (15.9)	−0.2 (−7.9 to 7.4)
Any serious adverse event	11 (6.1)	18 (9.8)	3.7 (−2.1 to 9.7)	14 (7.4)	1.3 (−4.2 to 6.9)
Death††	3 (1.7)	5 (2.7)	1.1 (−2.4 to 4.8)	1 (0.5)	−1.1 (−4.3 to 1.5)
Respiratory disability at wk 96 — no. (%)‡‡					
Grade on MRC breathlessness scale ≥3	0	2.7 (1.5)	1.5 (−0.5 to 3.5)	2.7 (1.4)	1.4 (−0.5 to 3.3)
FEV, <50% of predicted value	24.3 (13.4)	20.5 (11.1)	−1.1 (−8.7 to 6.4)	22.4 (11.8)	0.1 (−7.8 to 7.9)
Program-centered outcomes					
Treatment adherence§§					
Adherence within first 56 days — % of days	98.8±5.5	95.9±10.0	−2.9 (−4.6 to 1.3)	98.4±6.6	−0.5 (−1.7 to 0.8)
Cessation within first 56 days — no. (%)	1 (0.6)	3 (1.6)	—	1 (0.5)	—
Acquired drug resistance — no. (%)¶¶	0	0	—	2 (1.1)	—
Relapse-associated transmission risk‖‖					
Transmission risk period — days	0.5±4.3	2.4±8.3	1.9 (0.5 to 3.2)	3.2±14.1	2.7 (0.6 to 4.8)
New exposed household contacts — no.	0.01±0.15	0.01±0.10	0.00 (−0.03 to 0.03)	0.06±0.40	0.05 (−0.01 to 0.10)

DISCUSIÓN

- Pauta **BEDAQUILINA-LINEZOLID** no inferior a pauta estándar.
  - Consistente en diferentes subgrupos.
  - Duración acortada ⇨ mayor motivación y mejor adherencia.
  - Seguimiento exhaustivo ⇨ inconveniente ???
    - ✓ Experiencia positiva participantes.
    - ✓ Estudios futuros coste-efectividad.
    - ✓ No efectos secundarios graves ni dificultad respiratoria.
    - ✓ Detección precoz recurrencias/recaídas.

DISCUSIÓN

- Tasas resistencia concordantes ensayos previos
  - <1% a rifamicinas (pautas 4 meses).

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 384;18 NEJM.ORG MAY 6, 2021

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Cochrane Database of Systematic Reviews | Review - Intervention

Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis

Angeline G Grace, Abhenil Mittal, Siddharth Jain, Jaya P Tripathy, Srinath Satyanarayana, Prathap Tharyan, Richard Kirubakaran Authors' declarations of interest

Version published: 12 December 2019 Version history

- **Bedaquilina** (también clofazimina) ⇨ semividas largas ⇨ meses
  - Bacilos residuales viables en pautas cortas que generen resistencias...???
    - ✓ Solo 2 pacientes resistentes ⇨ 1.1%.
    - ✓ Incidencia 2% en regimenes de bedaquilina 6 meses.

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac029

JAC-Antimicrobial Resistance

Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review

Jahan Saeed Mallick[1]*, Parvati Nair[1], Elizabeth Tabitha Abbew[1,2], Armand Van Deun[3] and Tom Decroo[1]

[1]Institute of Tropical Medicine Antwerp, Department of Clinical Sciences, Kronenburgstraat 43, 2000 Antwerpen, Belgium; [2]Cape Coast Teaching Hospital, Interberton Road, Cape Coast, Ghana; [3]Independent consultant, Leuven, Belgium

THE LANCET Infectious Diseases

ARTICLES | VOLUME 22, ISSUE 4, P496-506, APRIL 2022

Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

Prof Nazir Ahmed Ismail, FCPath * Shaheed Vally Omar, PhD * Harry Moultrie, MBChB * Zaheda Bhyat, BTech Francesca Conradie, MBChB M Enwerem, MBBS et al. Show all authors Show footnotes

Junta de Castilla y León Consejería de Sanidad

Sacyl

Complejo Asistencial Universitario de León

DISCUSIÓN

- Seguimiento basado en la **clínica** y **cultivo de esputo** ⇨ PRAGMÁTICO.
- Enfoques futuros ⇨ sustituir cultivo:
  - Nuevos **biomarcadores de actividad** plasmáticos (RNA).

Clinical Infectious Diseases
MAJOR ARTICLE

Diagnostic Accuracy of the Cepheid 3-gene Host Response Fingerstick Blood Test in a Prospective, Multi-site Study: Interim Results

Jayne S. Sutherland,[1] Gian van der Spuy,[2] Awa Gindeh,[1] Nguyen Thuy Thuong Thuong,[3,4] AnnRitah Namuganga,[5] Olumuyiwa Owolabi,[1] Harriet Mayanja-Kizza,[5] Mary Nsereko,[5] Guy Thwaites,[3,4] Jill Winter,[6] Hazel M. Dockrell,[7] Thomas J. Scriba,[8] Annemieke Geluk,[9] Paul Corstjens,[10] Kim Stanley,[2] Tracy Richardson,[2] Jane A. Shaw,[2] Bronwyn Smith,[2] Stephanus T. Malherbe,[2] and Gerhard Walzl[2]; for the TrENDx-TB Consortium

THE LANCET
Respiratory Medicine

ARTICLES | VOLUME 8, ISSUE 4, P407-419, APRIL 2020

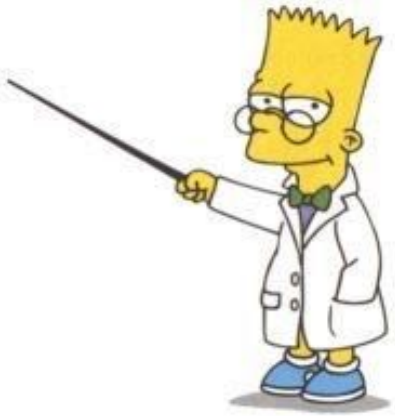
Blood transcriptional biomarkers for active pulmonary tuberculosis in a high-burden setting: a prospective, observational, diagnostic accuracy study

Carolin T Turner, Rishi K Gupta, Evdokia Tsaliki, Jennifer K Roe, Prasenjit Mondal, Georgina R Nyawo, Zaida Palmer, Robert F Miller, Byron WP Reeve, Grant Theron, Mahdad Noursadeghi

DISCUSIÓN

FORTALEZAS	LIMITACIONES
✓ Diseño pragmático.	❖ Diseño <u>abierto</u>: -Lo más fáctible pautas con diferente duración.
✓ Resultados aplicables en la clínica y para programas de tratamiento.	❖ <u>Sesgo de potencia</u>: -Algoritmo pre-especificado objetivo primario. -Evaluaciones estandarizadas. -Abandono insignificante.
✓ Multicéntrico y países con alta carga de TBC de ASIA.	❖ <u>No</u> inclusión <u>VIH</u> (se incluyen posteriormente) ⇨ evaluación adicional.

CONCLUSIONES



1

- ✓ Considerar cambio tratamiento TBC a estrategia con **duracion mínima necesaria** para la **curación** de la **mayoria de los pacientes**, prolongar tratamiento sólo en **enfermedad clínica persistente** y realizar seguimiento posterior para detectar **recaídas** y necesidad de **re-tratamiento.**

2

- ✓ Desarrollo de pautas terapéuticas nuevas, cortas, potentes así como biomarcadores de seguimiento que sean coste-efectivos.

3

- ✓ Implementación para evaluar resultados mediante programas de tratamiento individuales y poblacionales previo a estandarización.

Junta de Castilla y León Consejería de Sanidad · Sacyl · Complejo Asistencial Universitario de León

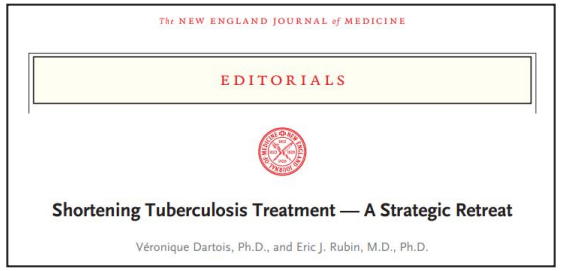
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

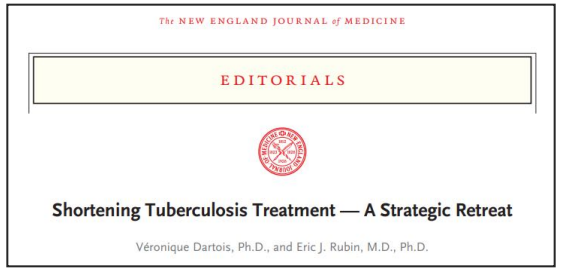
Shortening Tuberculosis Treatment — A Strategic Retreat

Véronique Dartois, Ph.D., and Eric J. Rubin, M.D., Ph.D.

N ENGL J MED 388;10 NEJM.ORG MARCH 9, 2023



- ✓ **Diseño complejo** ➡ no centrado en una sola pauta terapéutica frente comparador.
- ✓ Se **excluyeron grupos de alto riesgo** que luego se incluyen (cambio de criterios).
- ✓ Para **preservar poder estadístico** ➡ interrupción anticipada de 2 grupos.
  - ❑ **I de C más "laxo"** (menor de 12 puntos porcentuales) comparado con estudios previos.
- ✓ **Factores confusión** en conceptos
  - ❑ Seguimiento ➡ **ENFERMEDAD PERSISTENTE** (clínica y cultivo de esputo)
    - Negativo ➡ FIN tratamiento 8 semanas.
    - Positivo ➡ AMPLIACIÓN tratamiento 8 + 4 semanas ➡ FRACASO TERAPÉUTICO
    - Positivos tras 12 semanas tratamiento ➡ PAUTA ESTÁNDAR 24 semanas.
    - Recaída ➡ RETRATAMIENTO con PAUTA ESTÁNDAR según resistencias antimicrobianas.
- ✓ **Mucha adherencia** tanto tratamiento como seguimiento
  - ❑ MENOR adherencia = MAYOR fracaso terapéutico.



- ✓ **DESARROLLO RESISTENCIAS** con tratamiento acortados.
  - ❑ BEDAQUILINA sólo 2 casos.
    - Advertencia aumento mortalidad en ensayos previos.
    - Necesaria muestra mayor para extraer conclusiones.
  - ❑ LINEZOLID: toxicidad dosis, problema en otros ensayos.
- ✓ Estudios PAUTA ESTÁNDAR
  - ❑ **Recaída** tras **4 meses tratamiento rara**, incluso curaciones tras 2 meses tratamiento.
  - ❑ Seguimiento estrecho permita identificar pacientes que se beneficien pautas más largas.
- ✓ Nuevos estudios con pautas tratamiento acortadas con resultados superponibles al régimen estándar, incluso en situaciones de alta carga bacilífera serían beneficiosas países con escasos recursos:
  - ❑ Reducción costes, mejor adherencia y mayor satisfacción paciente.

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VOL. ■, NO. ■, 2023

EXPERT CONSENSUS DECISION PATHWAY

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

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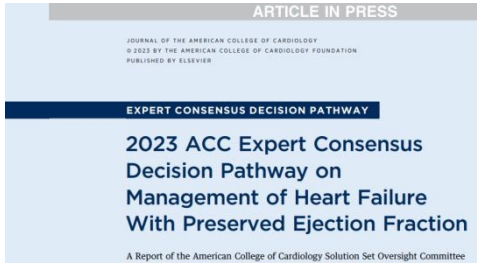
NECESIDAD CREAR ESTAS GUIAS



1. ✓ Cómo afrontamos a un paciente con disnea.
2. ✓ Cómo hacemos el diagnóstico y valoramos la necesidad de otros estudios.
3. ✓ Cómo reconocemos otras patologías que simulan una IC sin “colarnos” el diagnóstico.
4. ✓ Cómo manejamos las co-morbilidades y la pluripatologia.
5. ✓ Cómo iniciar y optimizar las opciones terapéuticas.
6. ✓ Cúando y cómo derivar a Cardiologia o Unidades de IC.
7. ✓ Cómo mejorar el acceso a la atención.
8. ✓ Cómo reconocer las diferencias específicas por sexo en el diagnóstico y tratamiento.

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ACTUACIÓN-MANEJO

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EXPERT CONSENSUS DECISION PATHWAY

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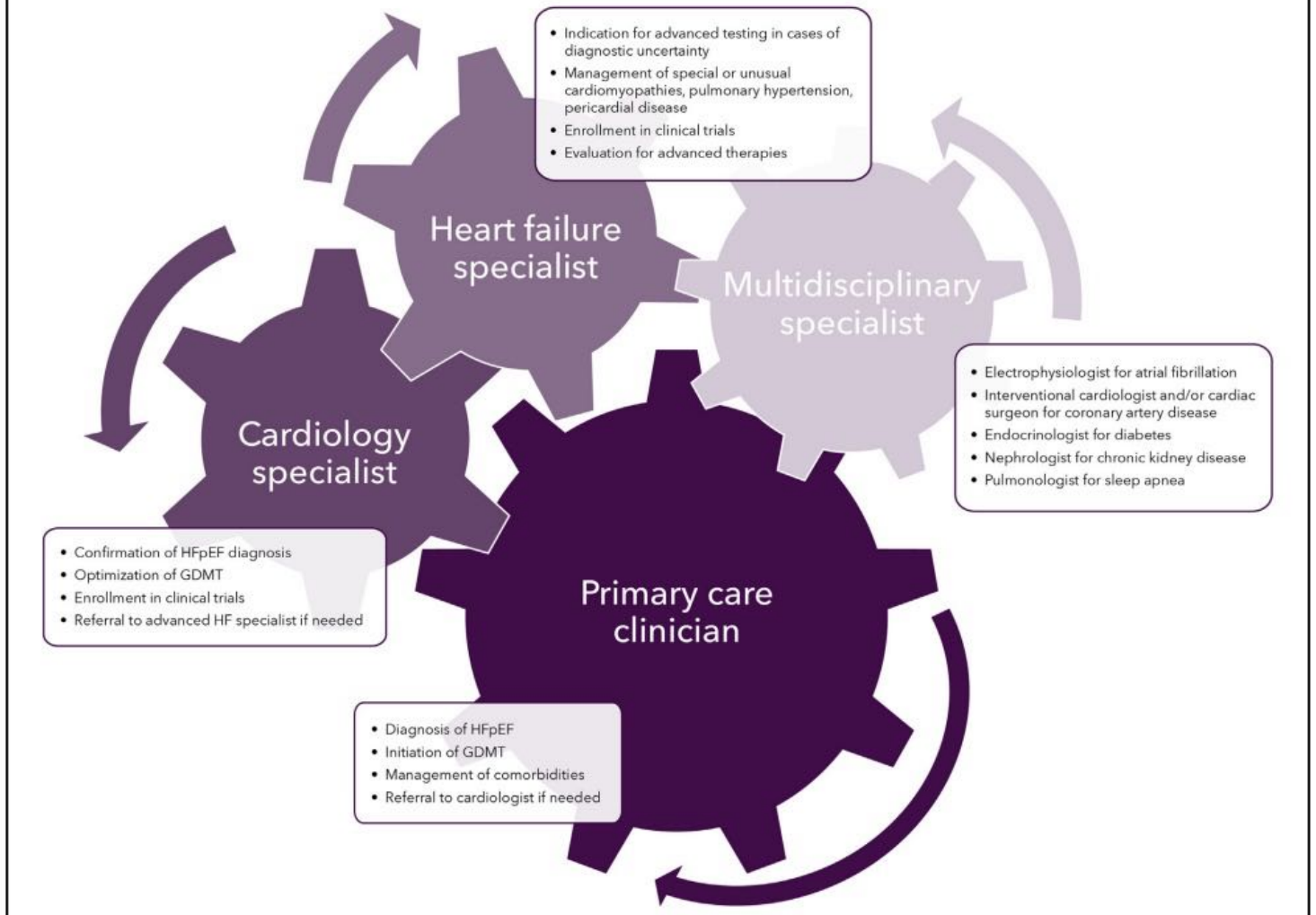
FIGURE 1 Approach to HFpEF



Abbreviations: GDMT = guideline-directed medical therapy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

DEFINICIÓN

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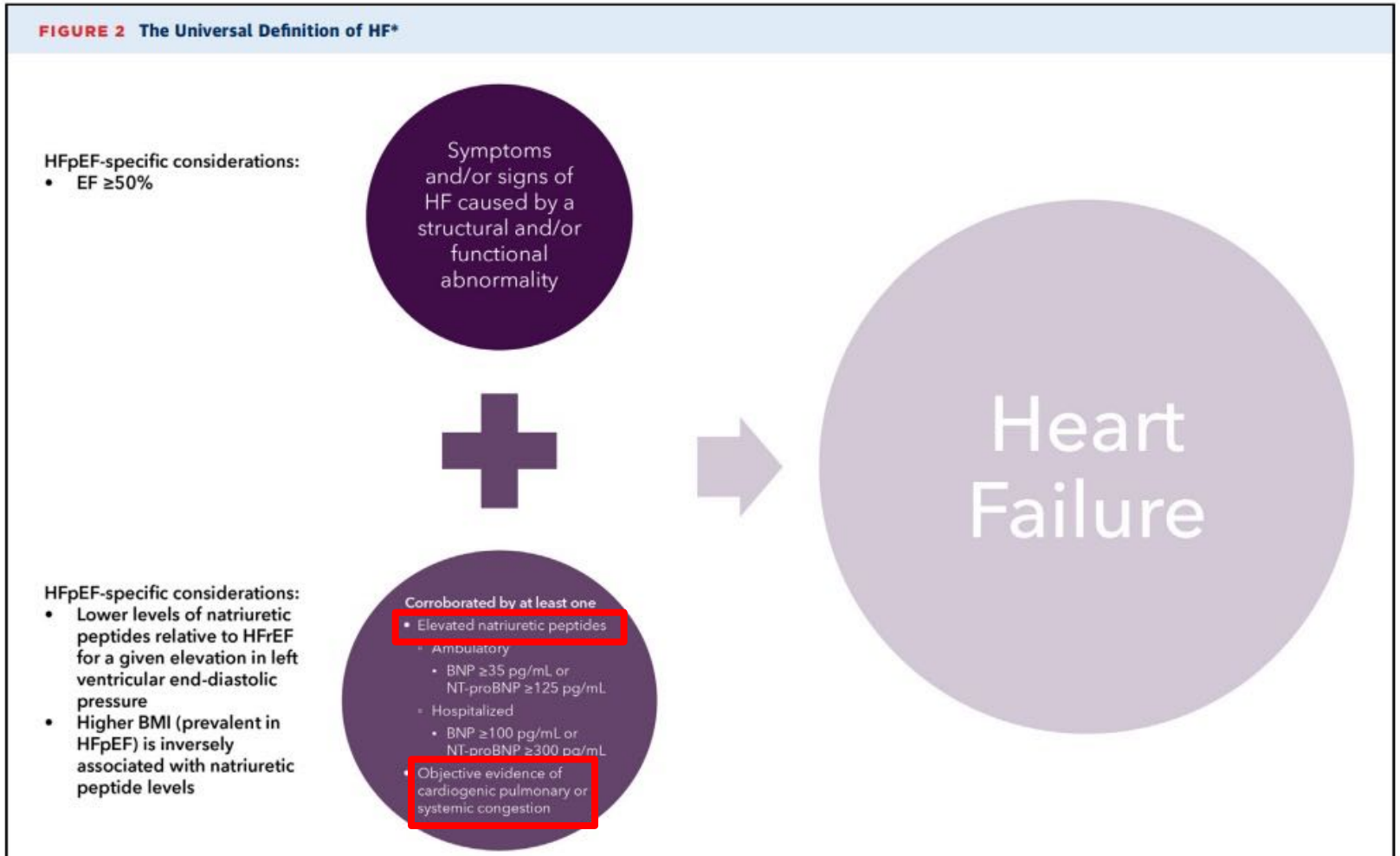
FIGURE 2 The Universal Definition of HF*



*The Universal Definition of HF requires symptoms and/or signs caused by structural/functional cardiac abnormalities *and* at least 1 of: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion. In HFpEF, specific additional criteria include EF 50% or greater, and consideration of pitfalls as described in the assessment of natriuretic peptide levels. BMI = body mass index; BNP = B-type natriuretic peptide; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

DEFINICIÓN

IC con FE reducida: **HFrEF**	Diagnóstico clínico IC y FE /< 40%.
IC con FE preservada: HFpEF	IC con FE >/ 50% no atribuible a otras causas: - Miocardiopatía infiltrativa. - Miocardiopatía hipertrófica. - Valvulopatías. - Patología pericardio. - IC por elevado GC.
IC con FE ligeramente deprimida: **HFmrEF**	IC con FE 41-49%.
IC con **FE mejorada**	IC con FE /<40% y a lo largo seguimiento > 40%.
IC con FE preservada simuladora: **HFpEF mimics**	IC con FE >/ 50% - Atribuida a causa primaria no cardiaca: - Enfermedad renal. - Hepatopatía. - Atribuida a causa cardiaca subyacente: - Miocardiopatía infiltrativa. - Miocardiopatía hipertrófica. - Valvulopatías. - Patologia pericardio. - IC por elevado GC.

NO ES SINÓNIMO de **DISFUNCIÓN DIASTÓLICA.**

DIAGNÓSTICO

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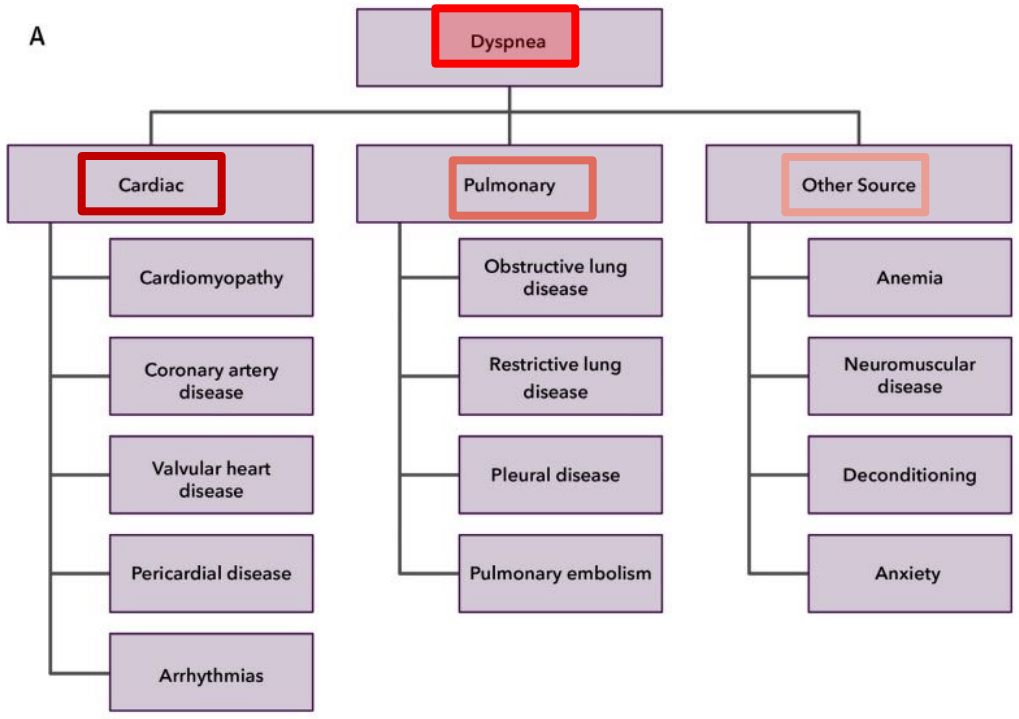
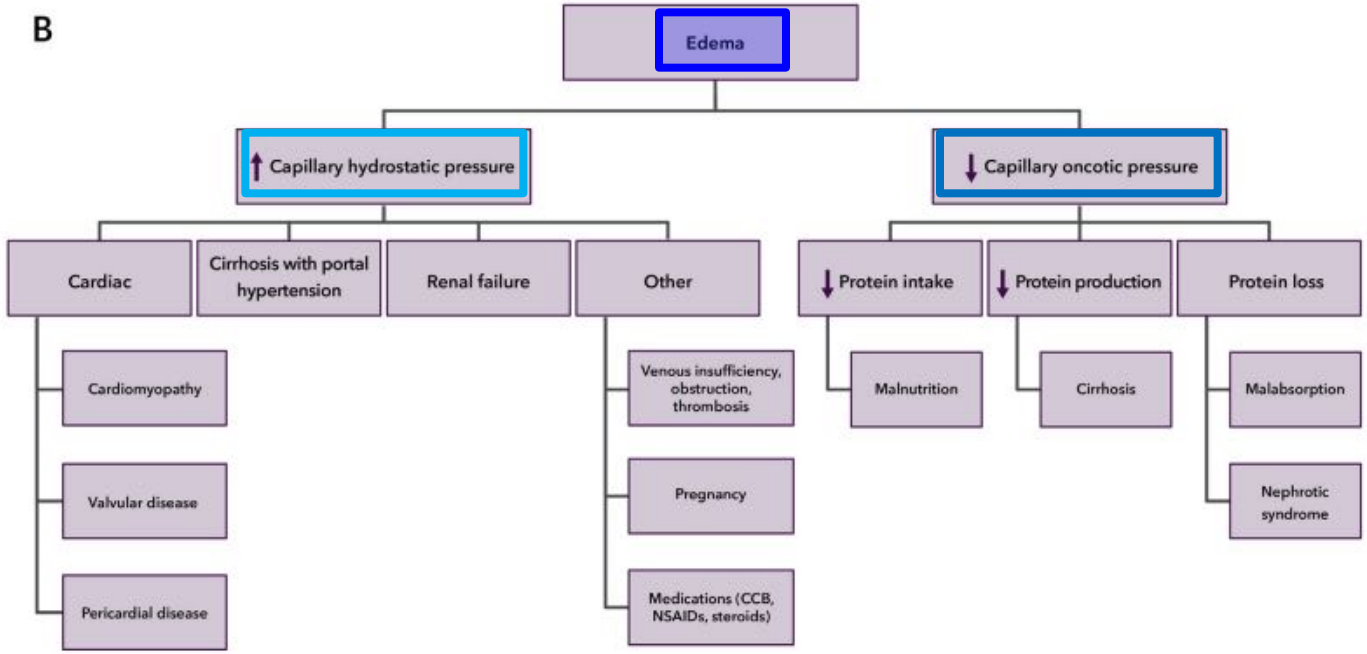
FIGURE 3 Differential Diagnosis of Dyspnea and Edema*



*However, other conditions can also cause these symptoms. **(A)** The differential diagnosis of dyspnea. **(B)** The differential diagnosis of edema. CCBs = non-dihydropyridine calcium-channel blockers; NSAIDs = nonsteroidal anti-inflammatory drugs.

FIGURE 3 Continued



DIAGNÓSTICO

SCORES DIAGNÓSTICOS

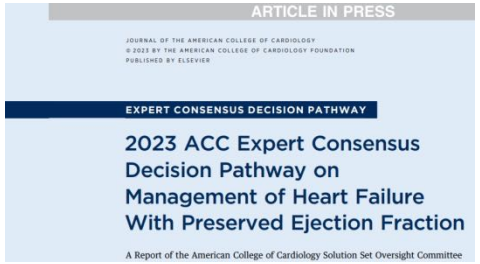


FIGURE 4 HFpEF Diagnostic Scoring Systems*

A

H_2FPEF

H_2	**H**eavy (BMI >30 kg/m²)	2
	On ≥2 anti**H**ypertensives	1
F	Atrial **F**ibrilllation	3
P	**P**ulmonary hypertension (PASP >35 mm Hg on Doppler echocardiography	1
E	**E**lder (age >60 years)	1
F	**F**illing pressure (E/e' >9 on Doppler echocardiography)	1

≥6 points: highly diagnostic of HFpEF

*(A) The H_2FPEF score includes 6 clinically accessible factors. (B) HFA-PEFF includes a more involved diagnostic algorithm starting with Pretest assessment, Echocardiographic and natriuretic peptide score, Functional testing for an advanced evaluation, and Final etiology assessment. BMI = body mass index; BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; CT = computed tomography; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; LAVI = left atrial volume index; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; PET = positron emission tomography; RWT = relative wall thickness; TR = tricuspid regurgitation.

DIAGNÓSTICO

SCORES DIAGNÓSTICOS

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2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction
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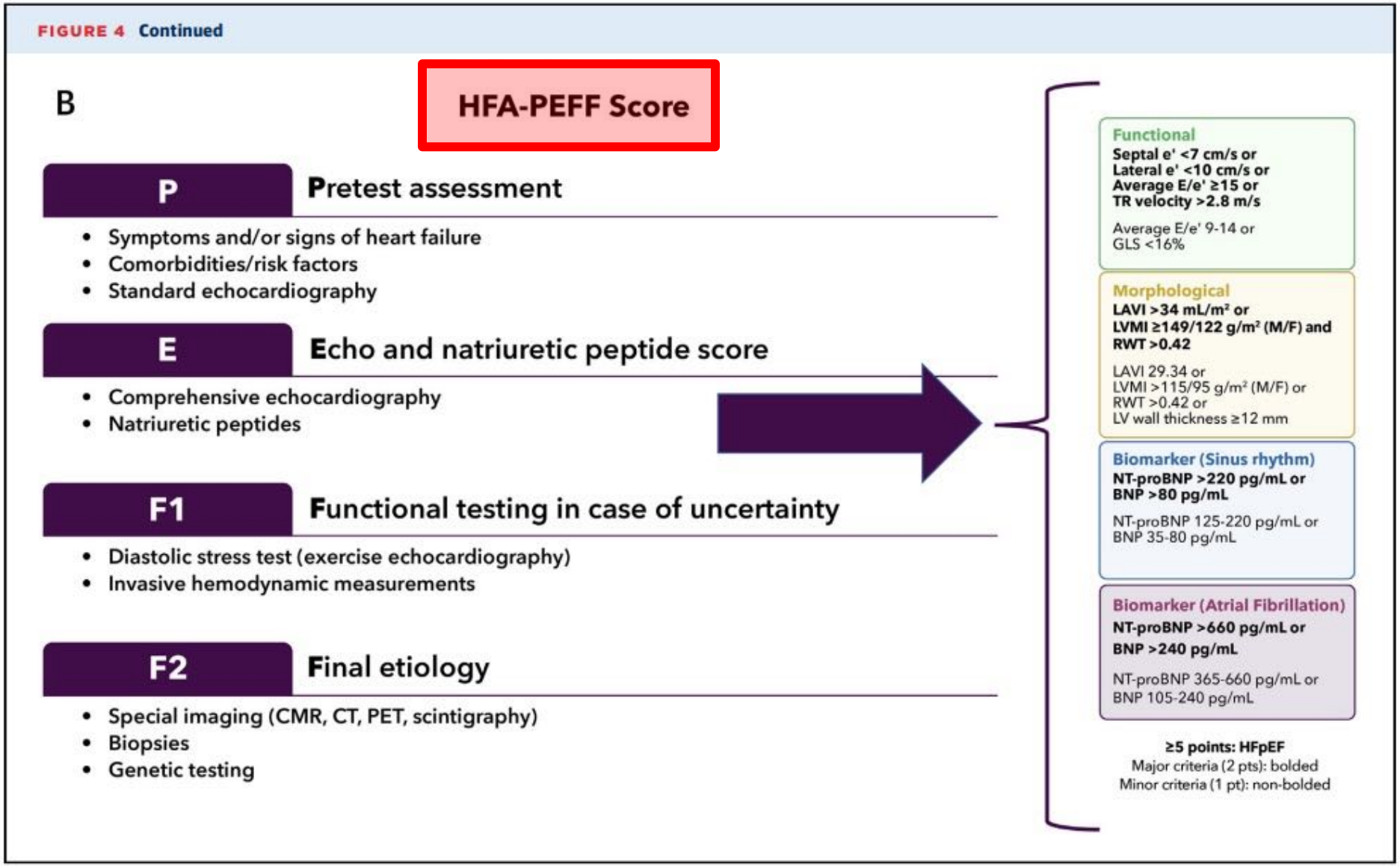


DIAGNÓSTICO

DIFERENCIAS SEXO

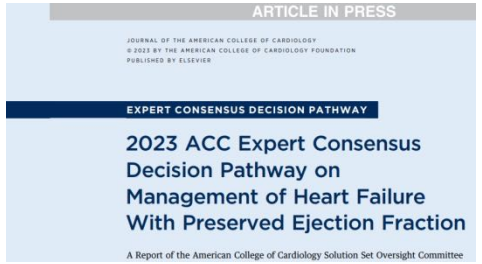
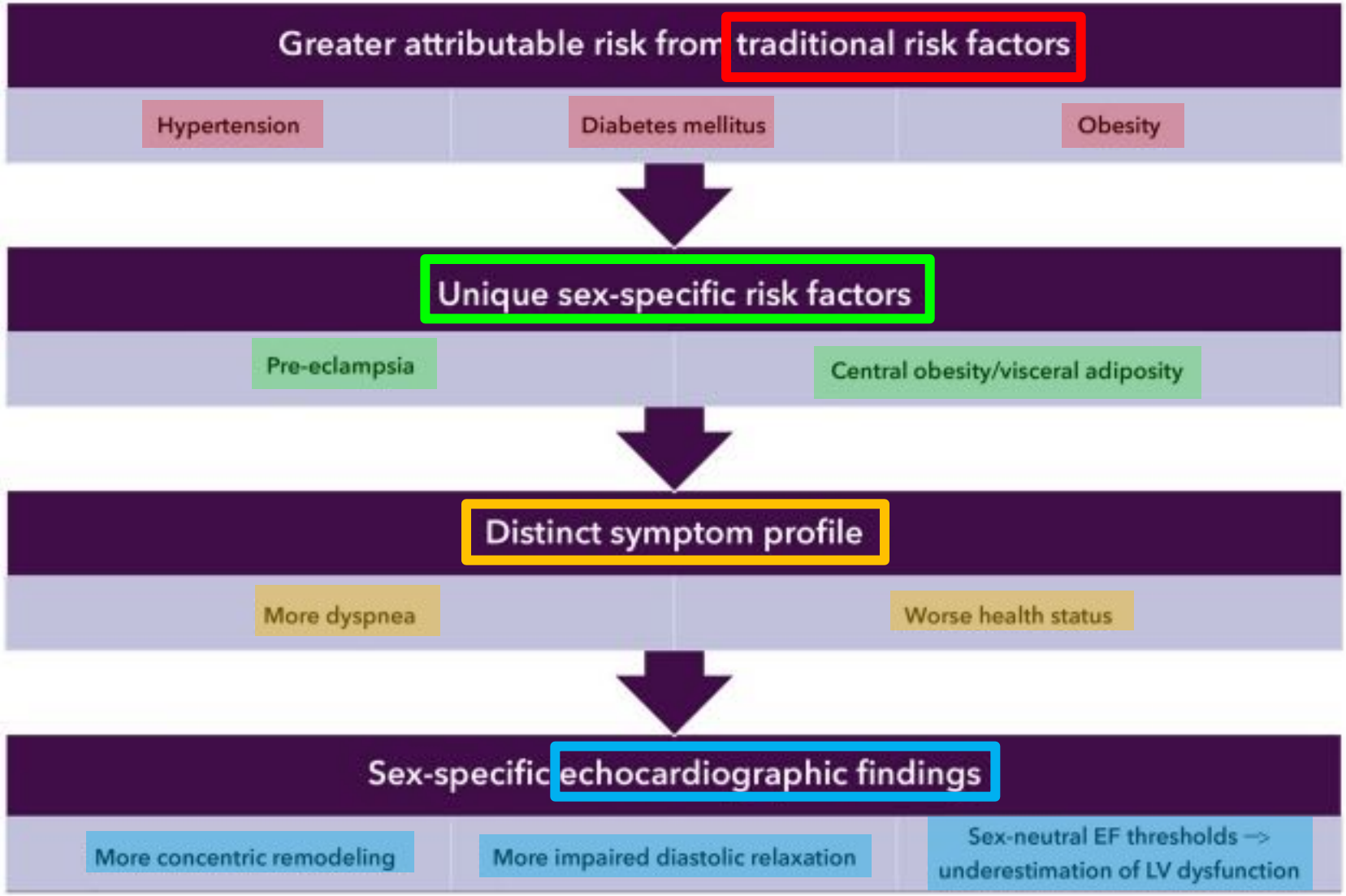


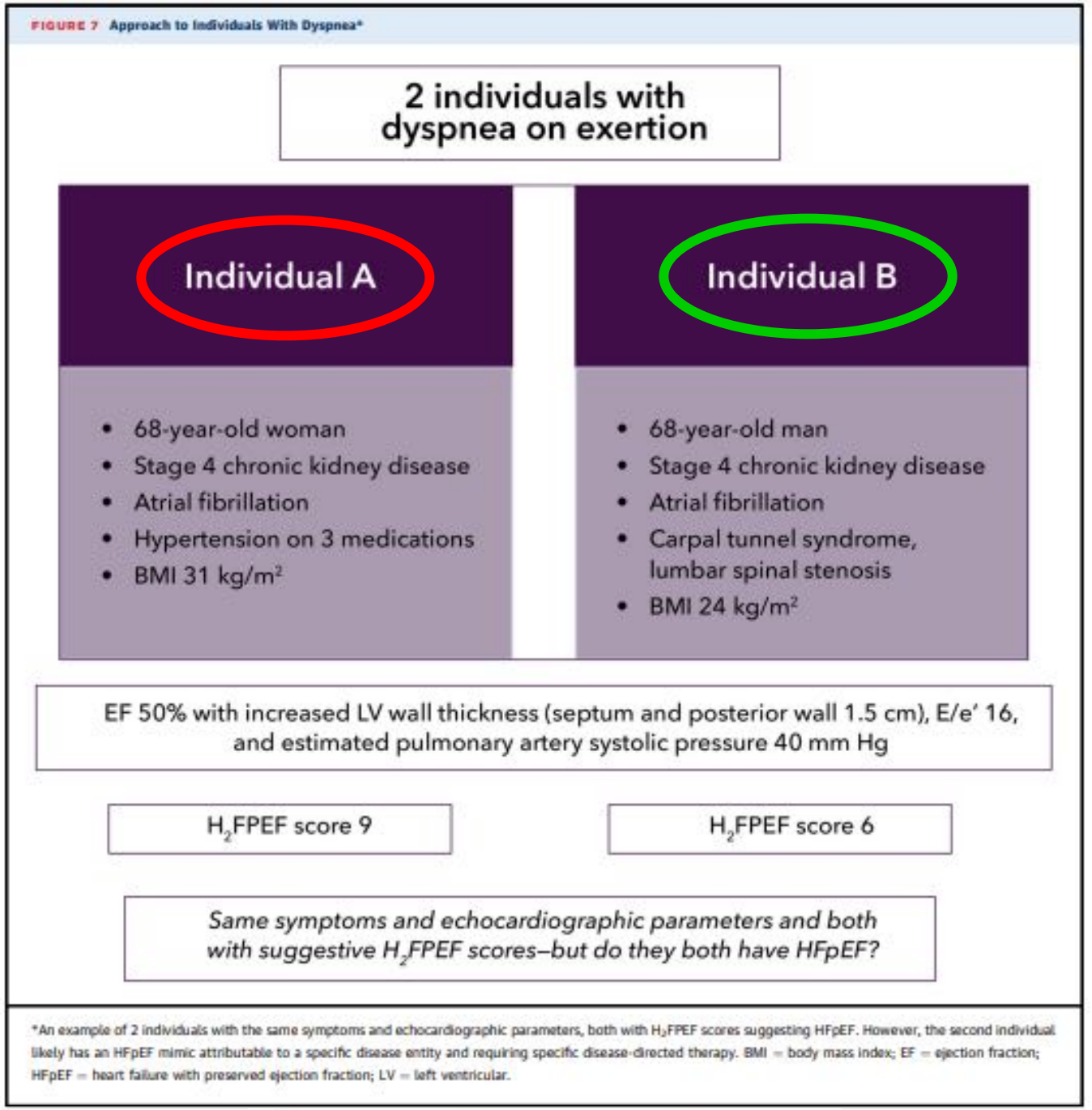
FIGURE 6 Sex-Specific Differences in Women: HFpEF Presentation and Diagnosis*



*Women with HFpEF have great attributable risk from traditional risk factors, unique risk factors, a distinct symptom profile, and distinct echocardiographic findings.
EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular.

DIAGNÓSTICO

- ✓ **IC FEp** con <u>comorbilidades asociadas</u>.



- ✓ **IC FEp** atribuida <u>causa específica</u>: **amiloidosis cardiaca por TTR.**
  - ➢ Necesarios estudios complementarios.

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DIAGNÓSTICO

CAUSAS SUBYACENTES POTENCIALMENTE TRATABLES

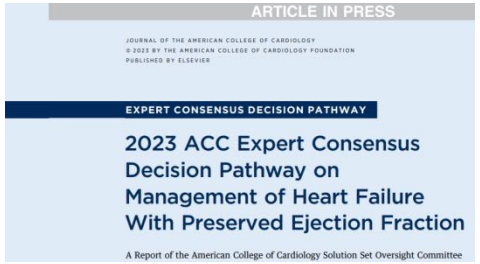


TABLE 1 Diagnostic Clues and Recommended Testing for HFpEF Mimics

HFpEF Mimic	Clinical Clues	Diagnostic Testing
Cardiac amyloidosis	Increased LV wall thickness Musculoskeletal issues (carpal tunnel syndrome, lumbar spinal stenosis) Neuropathy (sensory or autonomic)	Monoclonal protein screen (serum/urine immunofixation electrophoresis and serum free light chains) Technetium pyrophosphate scan (interpreted in the context of a negative monoclonal protein screen) Endomyocardial biopsy if monoclonal protein screen is positive
Hypertrophic cardiomyopathy	Unexplained LV hypertrophy LV outflow tract obstruction Family history	CMR if diagnosis is uncertain based on echocardiogram
Cardiac sarcoidosis	Extracardiac disease (pulmonary, ocular, dermatologic) High-degree atrioventricular block (especially if age <60 y) Ventricular arrhythmias	CMR FDG-PET scan Tissue biopsy (cardiac or extracardiac)
Hemochromatosis	Family history or history of frequent blood transfusions Diabetes Erectile dysfunction	Ferritin and transferrin *HFE* genetic testing CMR with T2* imaging
Fabry disease	Angiokeratomas Sensory neuropathy Proteinuria X-linked inheritance	Serum alpha-galactosidase level (in men) *GLA* genetic testing Biopsy of affected tissue
High-output HF	Echocardiogram with 4-chamber enlargement and/or increased LV outflow tract VTI	Investigate and treat underlying cause: anemia, arteriovenous malformations, cirrhosis, fistulas, thiamine deficiency
Myocarditis	Antecedent viral infection Elevated troponin in the absence of coronary artery disease Heart block and/or ventricular arrhythmias	CMR Endomyocardial biopsy
Pericardial disease	Prior cardiac surgery, chest radiation, or pericarditis Right-sided HF symptoms	CMR Right and left heart catheterization to demonstrate discordance in LV/RV pressure tracings during inspiration

CMR = cardiac magnetic resonance; FDG-PET = fluorodeoxyglucose-positron emission tomography; HF = heart failure; *HFE* = hereditary hemochromatosis gene; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; VTI = velocity time integral.

DIAGNÓSTICO

FIGURE 8 Stepwise Approach to Assessment of Individuals With Shortness of Breath and/or Edema

Patient with dyspnea and/or edema and EF ≥50%: Apply Universal Definition of HF

- ✓ Orina 24 horas con proteinuria, ecografia abdominal, GAB, espriometria....
- ✓ Anemia, cor pulmonale 2 enf. pulmonares, HTP primaria, SAOS/SAHS.

Noncardiac mimics
Is there a primary noncardiovascular entity causing symptoms?

YES → "Congestion primarily from" →
- Kidney disease
- Liver disease
- Chronic venous insufficiency

NO

HFpEF mimics
Does the patient's presentation warrant specific diagnostic assessment?

YES → "HF attributed to" →
- Infiltrative cardiomyopathy
- Hypertrophic cardiomyopathy
- Pericardial disease
- Valvular heart disease
- High-output heart failure

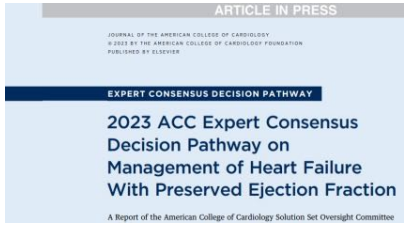
NO

HFpEF
Identify relevant comorbidities contributing to presentation that warrant treatment

→ "HFpEF associated with" →
- Hypertension
- Diabetes
- Atrial fibrillation
- Obesity
- Coronary artery disease
- Renal dysfunction

EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

TRATAMIENTO



ESTRATIFICACIÓN RCV y CONTROL FRCV

- HTA.
- DM.
- Obesidad.
- FA.
- Enferedad coronaria.
- SAOS.

TERAPIAS NO FARMACOLÓGICAS

- Dieta y ejercicio.
- Monitores arteria pulmonar implantabls inhalambricos.

TERAPIA FARMACOLÓGICA: control síntomas y F modificadores enfermedad.

- Diuréticos .
- ISGLT2.
- ARM.
- IRAN.
- ARA II.

TRATAMIENTO FARMACOLÓGICO

European Heart Journal (2006) 27, 2338–2345
doi:10.1093/eurheartj/ehl250

2006

Clinical research
Heart failure/cardiomyopathy

FASTTRACK The perindopril in elderly people with chronic heart failure (PEP-CHF) study

John G.F. Cleland[1]*, Michal Tendera[2], Jerzy Adamus[3], Nick Freemantle[4], Lech Polonski[5], and Jacqueline Taylor[6] on behalf of PEP-CHF Investigators

[1]Department of Cardiology, University of Hull, Castle Hill Hospital, Castle Road, Cottingham,Kingston upon Hull HU16 5JQ, UK; [2]Silesian School of Medicine, Katowice, Poland; [3]Department of National Defence, Warsaw, Poland; [4]University of Birmingham, Birmingham, UK; [5]Silesian School of Medicine, Zabrze, Poland; and [6]Glasgow Royal Infirmary, Glasgow, Scotland

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Volume 114, Issue 5, 1 August 2006; Pages 397-403
https://doi.org/10.1161/CIRCULATIONAHA.106.628347

2006

American Heart Association.

HEART FAILURE

Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure

The Ancillary Digitalis Investigation Group Trial

Ali Ahmed, MD, MPH, Michael W. Rich, MD, Jerome L. Fleg, MD, Michael R. Zile, MD, James B. Young, MD, Dalane W. Kitzman, MD, Thomas E. Love, PhD, Wilbert S. Aronow, MD, Kirkwood F. Adams, Jr, MD, and Mihai Gheorghiade, MD

The NEW ENGLAND JOURNAL of MEDICINE

2008

ORIGINAL ARTICLE

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., and Agata Ptaszynska, M.D., for the I-PRESERVE Investigators*

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2009

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Heart Failure

Clinical Effectiveness of Beta-Blockers in Heart Failure

Findings From the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) Registry

Adrian F. Hernandez, MD, MHS,*† Bradley G. Hammill, MS,*
Christopher M. O'Connor, MD, FACC,*† Kevin A. Schulman, MD,*† Lesley H. Curtis, PHD,*†
Gregg C. Fonarow, MD, FACC‡

Durham, North Carolina; and Los Angeles, California

ORIGINAL CONTRIBUTION

2013

ONLINE FIRST

Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

The NEW ENGLAND JOURNAL of MEDICINE

2015

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D., Gabe A. Koepp, M.H.A., Barry A. Borlaug, M.D., Horng H. Chen, M.D., Martin M. LeWinter, M.D., Susan M. Joseph, M.D., Sanjiv J. Shah, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Robert T. Cole, M.D., Gordon R. Reeves, M.D., Ryan J. Tedford, M.D., W.H. Wilson Tang, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Monica R. Shah, M.D., and Eugene Braunwald, M.D., for the NHLBI Heart Failure Clinical Research Network

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A Report of the American College of Cardiology Solution Set Oversight Committee

European Journal of Heart Failure (2017) 19, 1495–1503
doi:10.1002/ejhf.876

2017

RESEARCH ARTICLE

Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial

Michel Komajda[1]*, Richard Isnard[1], Alain Cohen-Solal[2], Marco Metra[3], Burkert Pieske[4], Piotr Ponikowski[5], Adriaan A. Voors[6], Fabienne Dominjon[7], Cécile Henon-Goburdhun[7], Matthieu Pannaux[8], and Michael Böhm[9], on behalf of the prEserveD left ventricular ejectIon fraction chronic heart Failure with ivabradine studY (EDIFY) Investigators†

[1]Department of Cardiology, University of Pierre and Marie Curie Paris VI, La Pitié-Salpêtrière Hospital, Paris, France; [2]UMR-S 942, Department of Cardiology, Paris Diderot University, Sorbonne Paris Centre, Lariboisière Hospital, Paris, France; [3]Department of Cardiology, University of Brescia, Brescia, Italy; [4]Department of Cardiology, Charité University, Berlin, Germany; [5]Department of Heart Diseases, Medical University and Centre for Heart Diseases, Military Hospital, Wrocław, Poland; [6]Department of Cardiology, University of Groningen, Groningen, the Netherlands; [7]Department of Cardiovascular Development, Institut de Recherches Internationales Servier (IRIS), Suresnes, France; [8]Department of Methodology and Data Valorisation, Institut de Recherches Internationales Servier (IRIS), Suresnes, France; and [9]Department of Cardiology, Universitätsklinken des Saarlandes, Klinikum für Innere Medizin III, Homburg/Saar, Germany

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The NEW ENGLAND JOURNAL of MEDICINE

2019

ORIGINAL ARTICLE

Effects of Serelaxin in Patients with Acute Heart Failure

M. Metra, J.R. Teerlink, G. Cotter, B.A. Davison, G.M. Felker, G. Filippatos, B.H. Greenberg, P.S. Pang, P. Ponikowski, A.A. Voors, K.F. Adams, S.D. Anker, A. Arias-Mendoza, P. Avendaño, F. Bacal, M. Böhm, G. Bortman, J.G.F. Cleland, A. Cohen-Solal, M.G. Crespo-Leiro, M. Dorobantu, L.E. Echeverría, R. Ferrari, S. Goland, E. Goncalvesová, A. Goudev, L. Køber, J. Lema-Osores, P.D. Levy, K. McDonald, P. Manga, B. Merkely, C. Mueller, B. Pieske, J. Silva-Cardoso, J. Špinar, I. Squire, J. Stępińska, W. Van Mieghem, D. von Lewinski, G. Wikström, M.B. Yilmaz, N. Hagner, T. Holbro, T.A. Hua,* S.V. Sabarwal, T. Severin, P. Szecsödy, and C. Gimpelewicz, for the RELAX-AHF-2 Committees Investigators†

TRATAMIENTO FARMACOLÓGICO

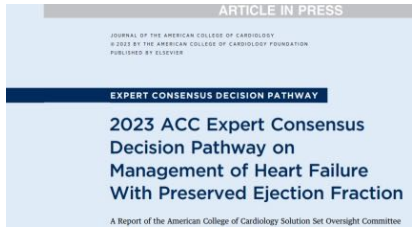
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TABLE 2 Selected Randomized Controlled Trials in Individuals With HFpEF

	DELIVER[6]	EMPEROR-PRESERVED[7]	TOPCAT*[16]	PARAGON-HF[19]	CHARM-PRESERVED[24]
Size	N = 6,263	N = 5,988	N = 3,445	N = 4,822	N = 3,023
Agent	Dapagliflozin	Empagliflozin	Spironolactone	Sacubitril/valsartan	Candesartan
Median age, y	72	72	69†	73	67
Female sex	44%	45%	52%	52%	40%
Median follow-up, y	2.3	2.2	3.3	2.9	3.1
EF entry criteria	>40%	>40%	≥45%	≥45%	>40%
Mean baseline LVEF	54%	54%	56%†	58%	54%
Proportion with T2DM	45%	49%	33%	43%	29%
HF medical therapy					
Diuretic agent	77%	NR	82%	95%	75%
ACE inhibitor or ARB	73%	81%	84%	86%	19%‡
ARNI	5%	2%	N/A	N/A	N/A
Beta-blocker	83%	86%	78%	80%	56%
MRA	43%	37%	N/A	26%	12%
Primary composite outcome, HR or rate ratio (95% CI)	Worsening HF and CV death: HR: 0.82 (0.73-0.92)	Hospitalization for HF and CV death: HR: 0.79 (0.69-0.90)	Hospitalization for HF, aborted cardiac arrest, CV death: HR: 0.89 (0.77-1.04)	Total hospitalizations for HF and CV death: Rate ratio: 0.87 (0.75-1.01)	Hospitalization for HF and CV death: HR: 0.86 (0.74-1.00)
Hospitalization for HF, HR or rate ratio (95% CI)	HR: 0.77 (0.67-0.89)	HR: 0.71 (0.60-0.83)	HR: 0.83 (0.69-0.99)	Rate ratio: 0.85 (0.72-1.00)	HR: 0.84 (0.70-1.00)
Urgent visit for HF, HR (95% CI)	0.76 (0.55-1.07)	NR	NR	NR	NR
CV death, HR (95% CI)	0.88 (0.74-1.05)	0.91 (0.76-1.09)	0.90 (0.73-1.12)	0.95 (0.79-1.16)	0.95 (0.76-1.18)

All trials were placebo-controlled, except for PARAGON-HF, which compared sacubitril/valsartan to valsartan.

*A significant reduction in the primary composite outcome was observed in participants enrolled in North America (HR: 0.82; 95% CI: 0.69-0.98), whereas no benefit was observed in the overall population or among those enrolled in Russia/Georgia (HR: 1.10; 95% CI: 0.79-1.51).

†Reported as median.

‡ACE inhibitor use only.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; N/A = not applicable; NR = not reported; T2DM = type 2 diabetes mellitus.

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TABLE 3 Starting and Target Doses of Select GDMTs for HFpEF

Drug Class	Starting Dose	Target Dose
SGLT2is		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Aldosterone antagonists		
Spironolactone	25 mg daily	50 mg daily
ARNIs		
Sacubitril/valsartan	24 mg/26 mg twice daily	97 mg/103 mg twice daily
ARBs		
Candesartan	4 mg to 8 mg daily	32 mg daily

ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium-glucose cotransporter-2.

- ✓ Según:
  - ❑ PA.
  - ❑ FG.
  - ❑ Potasio.
- ✓ Seguimiento periódico
  - ❑ 2 semanas.
  - ❑ 2 meses.

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

Lancet 2022; 400: 1938–52
Published Online

Summary
Background There is a paucity of evidence for dose and pace of up-titration of guideline-directed medical therapies after admission to hospital for acute heart failure.

Lancet 2022; 400: 1938–52

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TABLE 4 Contraindications and Cautions for SGLT2i, MRAs, ARNIs, and ARBs

Drug Class	Contraindications	Cautions
SGLT2i	Type 1 diabetes mellitus (limitation to use) Lactation On dialysis Known hypersensitivity	Kidney impairment: For dapagliflozin, eGFR <25 mL/min/1.73 m^2 For empagliflozin, eGFR <20 mL/min/1.73 m^2 Pregnancy Increased risk of mycotic genital infections May contribute to volume depletion or hypotension Ketoacidosis (including euglycemic) in individuals with poorly controlled diabetes, dehydration, or fasting Acute kidney injury Necrotizing fasciitis of the perineum (Fournier's gangrene) is rare but can be serious and life-threatening
MRA	Potassium ≥5.0 mmol/L Addison disease Pregnancy Known hypersensitivity	Kidney impairment: Avoid if eGFR <30 mL/min/1.73 m^2 or serum creatinine ≥2.5 mg/dL Initiate at half dose if eGFR 30 to 50 mL/min/1.73 m^2 Concomitant use with drugs and supplements that increase serum potassium, such as: Potassium supplementation ACE inhibitors, ARBs, or ARNIs NSAIDs Trimethoprim Gynecomastia (consider use of eplerenone) Lactation
ARNI	Coadministration within 36 h of ACE inhibitor use History of any angioedema Pregnancy/lactation Severe (Child-Pugh C) hepatic impairment Known hypersensitivity Use of aliskiren in individuals with diabetes mellitus	Reduce the starting dose to half the usually recommended starting dose if: Not currently taking an ACE inhibitor or ARB or taking a low dose of an ACE inhibitor or ARB Moderate (Child-Pugh B) hepatic impairment Renal artery stenosis Hypotension
ARB	Pregnancy/lactation Avoid concomitant use with an ACE inhibitor, aliskiren, or ARNI Known hypersensitivity Renal artery stenosis	History of any angioedema Hyperkalemia Hypotension Acute kidney injury

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid antagonists; NSAIDs = nonsteroidal anti-inflammatory drugs; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

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DIFERENCIAS SEXO

✓ **ISGLT2** ⇨ mismo beneficio.

✓ **SACUBITRIL/VALSARTAN** y **ESPIRONOLACTONA**: con cualquier FE

- Anatómicamente tamaño VI menor ⇨ sobreestimada FE.
- FE 50-55% ⇨ baja comparada con hombres .
  - Diferencias respuesta tratamientos con efectos sobre sistema neurohormonal.

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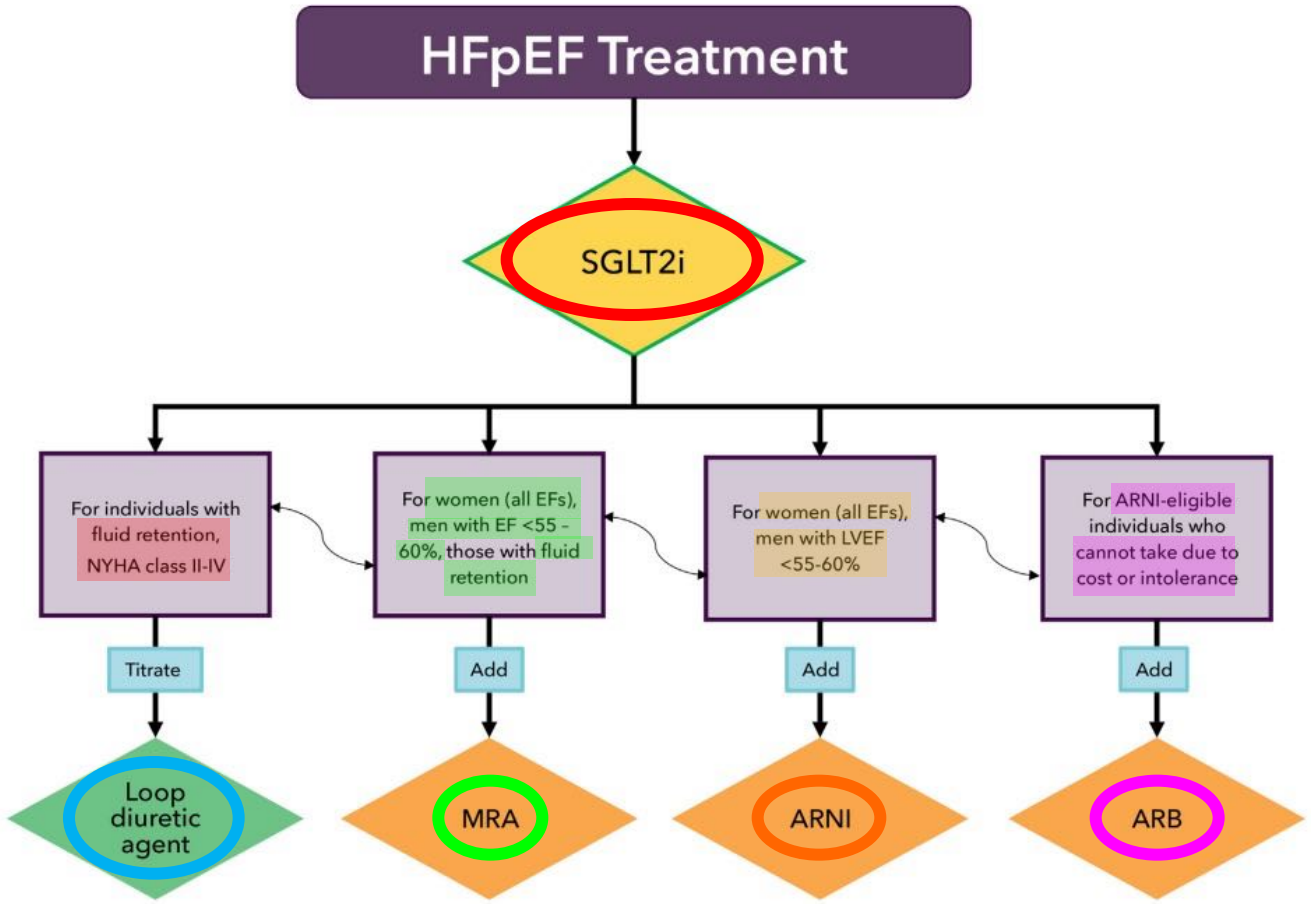
FIGURE 9 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF*



*Green color identifies a Class 1 therapy from clinical practice guidelines,[14] yellow color indicates a Class 2a therapy, and orange color denotes a Class 2b therapy. SGLT2is receive a Class 2a indication in the 2022 AHA/ACC/HFSA HF Guidelines,[14] but the benefit, now confirmed in 2 randomized trials,[60,61] suggests that SGLT2is may receive a stronger class of recommendation in future guidelines, and thus the box is shaded yellow with a green border. AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

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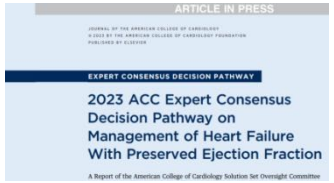
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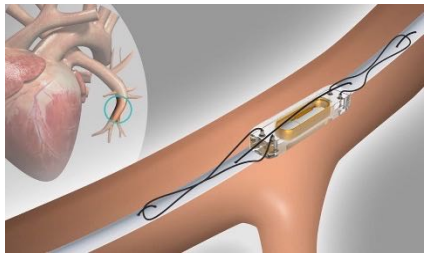
TABLE 5 Nonpharmacological Interventions in HFpEF

Study	Sample Size (HFpEF only)	Intervention	Outcome
WEIGHT LOSS AND/OR EXERCISE TRAINING			
Edelmann et al[84]	64	3 months of endurance/resistance training	■ Peak Vo_2 increased by 3.3 mL/kg/min ■ Improved quality of life ■ Improvement in E/e' and left atrial volume index
Mueller et al[85]	176	12 weeks of high-intensity interval training and moderate continuous training	■ Improved peak Vo_2 at 3 months
Kitzman et al[86]	63	16 weeks of exercise training	■ Peak Vo_2 increased by 2 mL/kg/min ■ Improved quality of life
Kitzman et al[87]	100	20 weeks of caloric restriction, aerobic exercise, or both	Increase in peak Vo_2 by: ■ Exercise: 1.2 mL/kg/min ■ Diet: 1.3 mL/kg/min ■ Both (additive): 2.5 mL/kg/min
Brubaker et al[88]	88	20 weeks of (caloric restriction and aerobic exercise) ± resistance training	Addition of resistance training to caloric restriction and aerobic exercise ■ increase in leg strength and muscle quality ■ no additive increase in peak Vo_2 or QOL
Mikhalkova et al[89]	12 (all women)	Gastric bypass	■ Improvement in Minnesota Living with Heart Failure score ■ Improved diastolic relaxation on echocardiogram
DEVICE THERAPIES			
Adamson et al[90,91]	119	Implantable pulmonary artery monitor	50% reduction in HF hospitalization with mean follow-up of 17.6 months
Lindenfeld et al[92]	795	Implantable pulmonary artery monitor	No reduction in all-cause mortality, HF hospitalizations, and urgent HF visits.

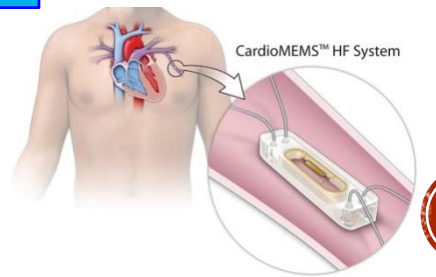
HF = heart failure; HFpEF = heart failure with preserved ejection fraction; Vo_2 = oxygen consumption

- ✓ >1 Hospitalización y mantener CF III/IV NYHA a pesar tratamiento óptimo.
- ✓ Labilidad en cuanto a congestión a pesar de supervisón estrecha.
- ✓ Síndrome cardio-renal.
- ✓ Comorbilidades que presenten dificultad diferenciar etiología disnea (obesidad, EPOC...).



CHAMPION

GUIDE-HF



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FACTORES DE RIESGO Y COMORBILIDADES

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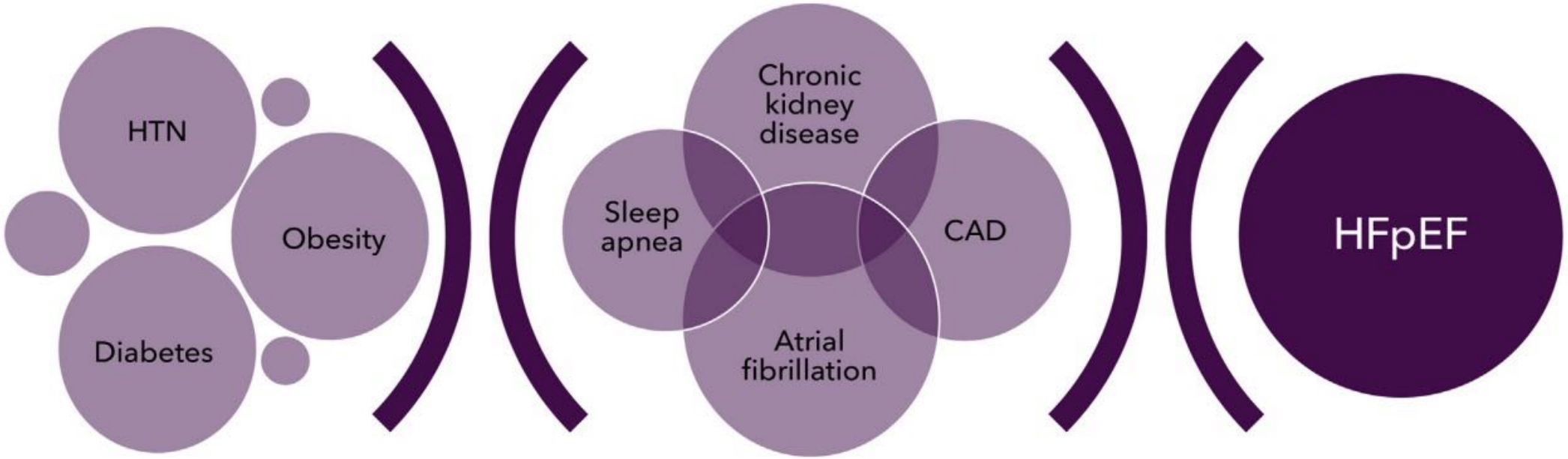
FIGURE 10 Interplay of HFpEF Comorbidities*



*Hypertension, diabetes mellitus, and obesity can result in coronary artery disease, atrial fibrillation, sleep apnea, and chronic kidney disease. Chronic kidney disease and sleep apnea can, in turn, worsen hypertension. These factors all influence the pathogenesis and outcomes of individuals with HFpEF. CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension.

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FACTORES DE RIESGO Y COMORBILIDADES

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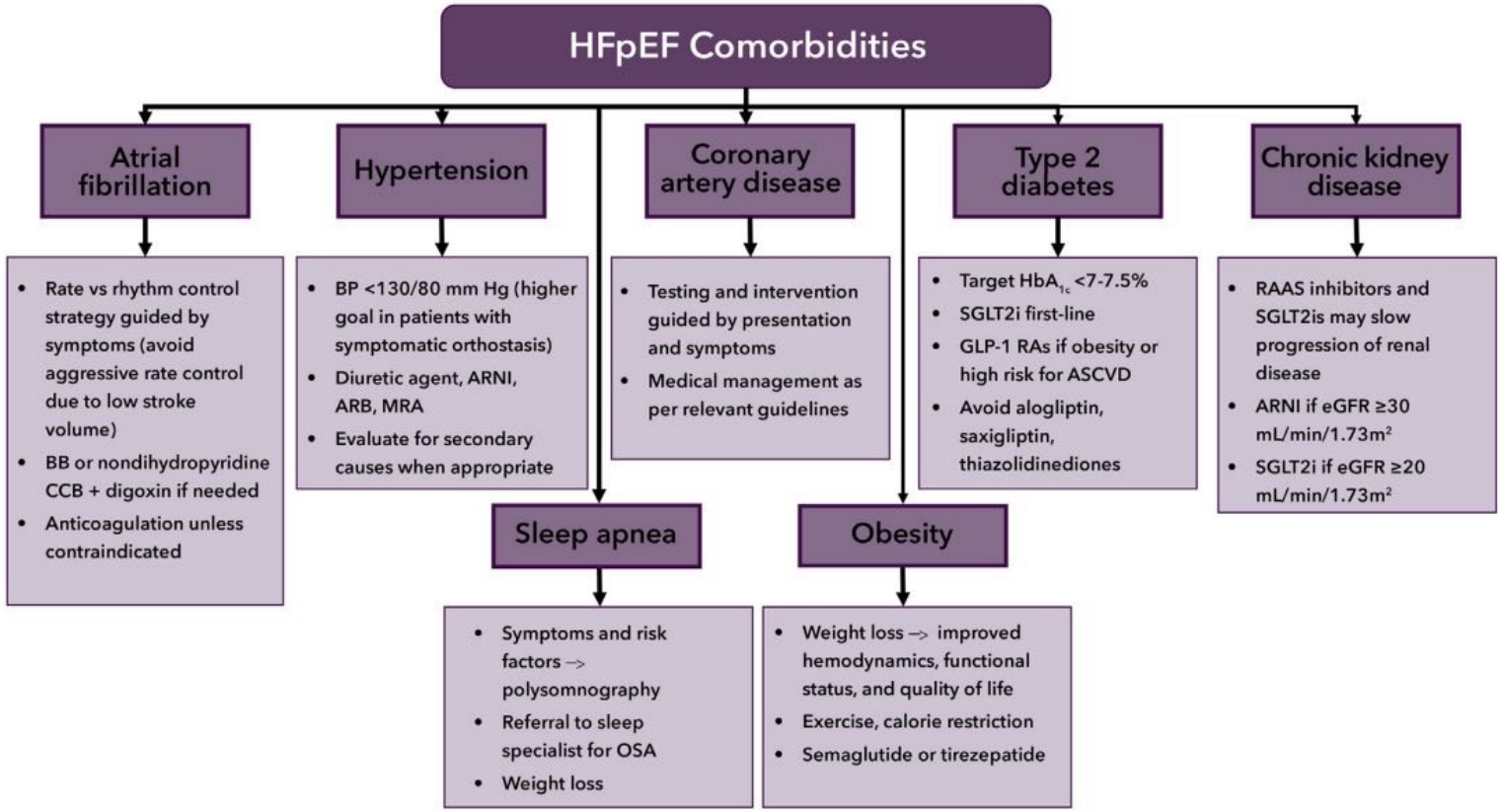
FIGURE 11 Management of Comorbidities Associated With HFpEF



ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BB = beta-blocker; BP = blood pressure; CCB = calcium-channel blocker; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonist; HbA_{1c} = glycosylated hemoglobin; MRA = mineralocorticoid antagonist; OSA = obstructive sleep apnea; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

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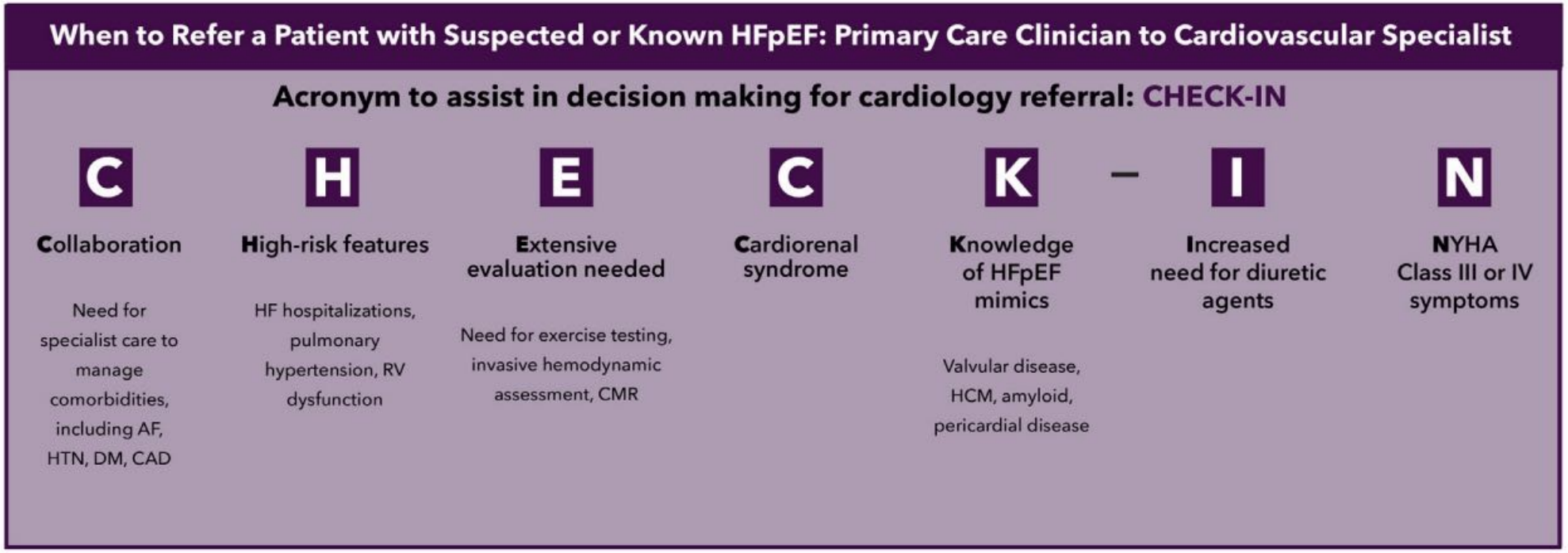
FIGURE 12 CHECK-IN: When to Refer a Patient With Suspected or Known HFpEF: Primary Care Clinician to Cardiovascular Specialist*



*Most individuals with suspected or proven HFpEF should be considered for referral to a cardiovascular specialist or advanced HF practice. Features to assist in timing of referral are summarized in the acronym *CHECK-IN*, which includes aspects of medical and HF complexity. AF = atrial fibrillation; CAD = coronary artery disease; CMR = cardiac magnetic resonance; DM = diabetes mellitus; HF = heart failure; HCM = hypertrophic cardiomyopathy; HTN = hypertension; NYHA = New York Heart Association; RV = right ventricular.

MANEJO

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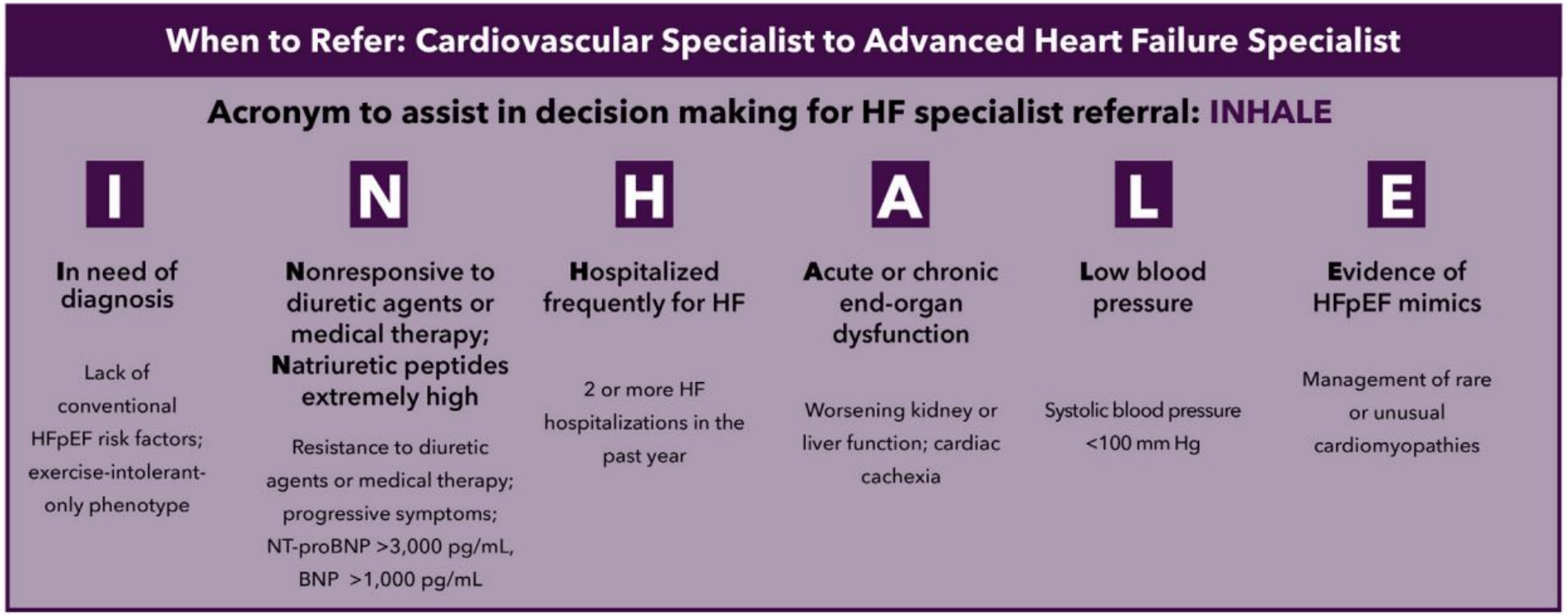
FIGURE 13 **INHALE: Acronym for Advanced HF Specialist Referral***



*Most individuals with suspected or proven HFpEF can be managed by a general cardiovascular specialist. However, there are some situations that suggest a special or unusual cardiomyopathy (such as infiltrative or restrictive cardiomyopathy), pulmonary hypertension, or pericardial disease. Features to assist in identification of individuals with advanced HF not classic for HFpEF are summarized in the acronym "INHALE," which includes markers of advanced HF. BNP = B-type natriuretic peptide; BP = blood pressure; HF = heart failure; HFPEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

MANEJO INTERDISCIPLINAR

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FIGURE 14 The Essential Skills of a Care Team

EP = electrophysiology; GDMT = guideline-directed medical therapy; HF = heart failure.

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Take Home Messages

FIGURE 15 Checklist for Communication to Clinicians Involved in Continuing Care

Hospital course	• Reason for admission
	• Sentinel symptoms
	• Congestion status
	  ◦ Objective assessment of volume status
	  ◦ Admission and discharge weight
	  ◦ Diuretic agent dosing
	  ◦ Rescue diuretic dosing
	• Unexpected events

Planned therapies and monitoring	• Plan for GDMT optimization • Plan to monitor electrolytes and kidney function • Follow-up for pending or planned diagnostic tests
Follow-up related to comorbidities	• Chronic kidney disease • Sleep-disordered breathing • Diabetes • Atrial fibrillation • Coronary artery disease • Obesity • Anemia
Advance care planning	• Prognostic assessment • Palliative care referral

Adapted from Hollenberg et al.[56] GDMT = guideline-directed medical therapy.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

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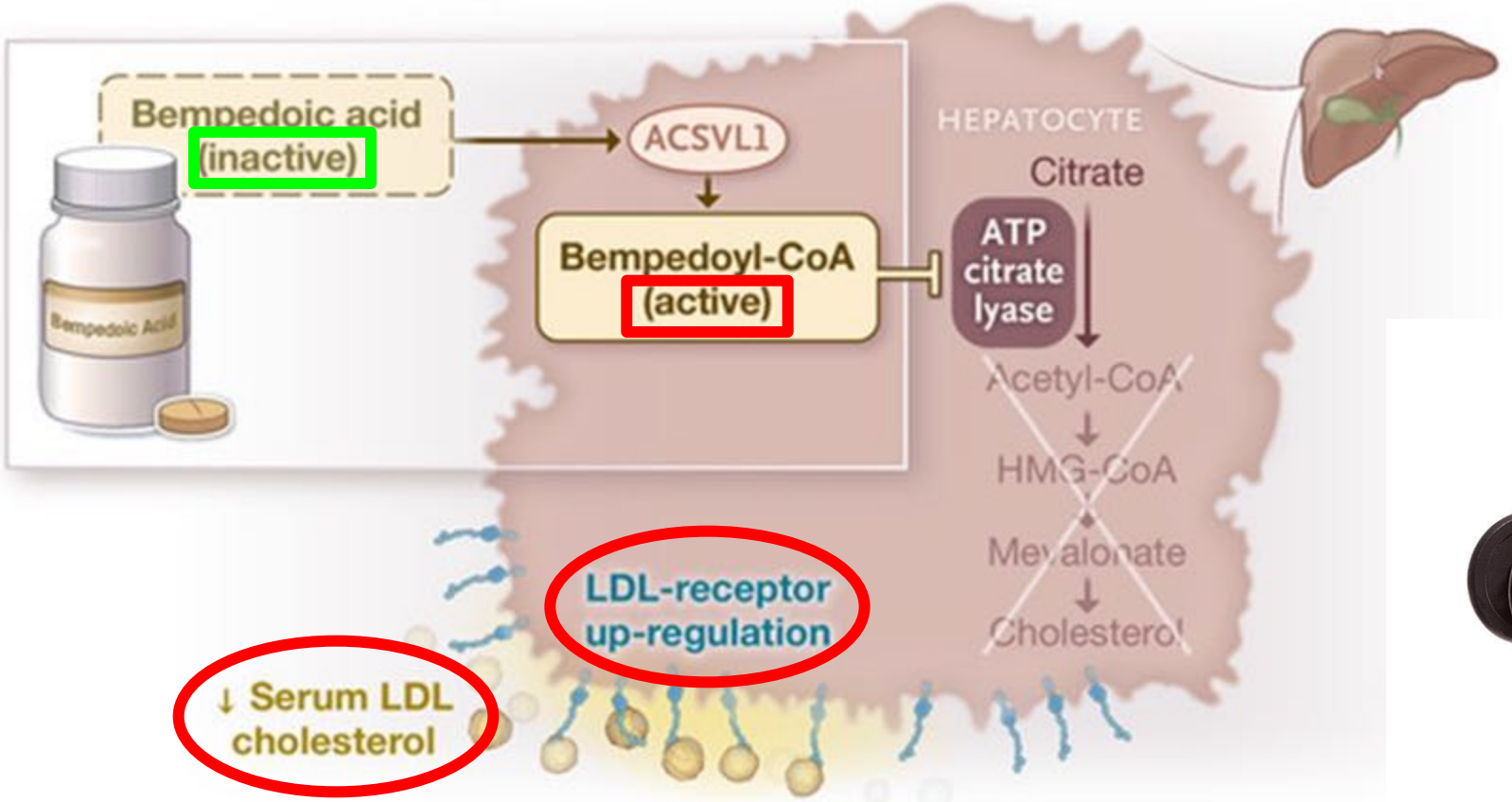
INTRODUCCIÓN



INTRODUCCIÓN

- Reducción LDLc 17 a 28%.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

Research

JAMA | Original Investigation

Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease

The CLEAR Wisdom Randomized Clinical Trial

Anne C. Goldberg, MD; Lawrence A. Leiter, MD; Erik S. G. Stroes, MD, PhD; Seth J. Baum, MD; Jeffrey C. Hanselman, MS; LeAnne T. Bloedon, MS, RD; Narendra D. Lalwani, PhD, MBA; Pragna M. Patel, PharmD; Xin Zhao, MD, MA; P. Barton Duell, MD

Atherosclerosis 277 (2018) 195–203

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Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

ORIGINAL RESEARCH

American Heart Association.

Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study

Christie M. Ballantyne [a,*], Maciej Banach [b], G.B. John Mancini [c], Norman E. Lepor [d,e], Jeffrey C. Hanselman [f], Xin Zhao [f], Lawrence A. Leiter [g]

[a] Department of Medicine, Baylor College of Medicine, One Baylor Plaza, BCM 285, Houston, TX, 77030, USA
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[c] Division of Cardiology, University of British Columbia, 2775 Laurel Street 10th Floor, Vancouver, V5Z 1M9, British Columbia, Canada
[d] David Geffen School of Medicine at UCLA and Cedars-Sinai Medical Center, Los Angeles, CA, USA
[e] Westside Medical Associates of Los Angeles, 99 La Cienega Blvd. #203, Beverly Hills, CA, 90211, USA
[f] Clinical Development, Esperion Therapeutics, Inc., 3891 Ranchero Dr., Ann Arbor, MI, 48108, USA
[g] Division of Endocrinology & Metabolism, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, 61 Queen St East #6121, Toronto, M5C 2T2, Ontario, Canada

Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance

Ulrich Laufs, MD, PhD; Maciej Banach, MD, PhD; G. B. John Mancini, MD; Daniel Gaudet, MD, PhD; LeAnne T. Bloedon, MS, RD; Lulu Ren Sterling, PhD; Stephanie Kelly, BS; Erik S. G. Stroes, MD, PhD

- No ensayos aleatorizados y controlados en **enfermedad cardiovascular.**

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MÉTODOS

- **CLEAR:** Cholesterol Lowering via Bempedoic Acid and ACL-Inhibiting Regimen
  - Efectos ácido bempedoico en eventos cardiovasculares en una población "mezclada" con indicación de tratamiento en prevención primaria y secundaria con intolerancia a dosis estatinas indicadas según guías.

- Ensayo aleatorizado, doble ciego y controlado con placebo.
  - 32 paises, 1250 centros.

Spain	
Maria Del Carmen Cuesta Mayor	Nuevas tecnologias en Diabetes y Endocrinologia, Sevilla
Jose Ramon Gonzalez Juanatey	Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, La Coruña
Rafael Hidalgo Urbano	Hospital Universitario Virgen Macarena, Sevilla
Manuel Jimenez Navarro	Hospital Clinico Universitario Virgen de la Victoria, Málaga
Manuel Martinez Selles	Hospital General Universitario Gregorio Maranon, Madrid
Cesar Morcillo Serra	Hospital SANITAS CIMA, Barcelona
Margarita Rivas	Hospital Infanta Luisa, Sevilla
Violeta Rodriguez Rodriguez	Hospital Virgen del Mar, Almeria
Juan Roldan Sanchez	Institut Catala de Serveis Medics, Girona
Marcelo Sanmartin Fernandez	Sanmartin Fernandez, Marcelo, Madrid
Alessandro Sionis	Hospital de la Santa Creu i Sant Pau, Barcelona

MÉTODOS

POBLACIÓN ELEGIBLE

CRITERIOS DE INCLUSIÓN

Pacientes 18 a 85 años

PREVENCIÓN PRIMARIA

Elevado riesgo CV

- Reynolds risk score > 30% o SCORE risk > 7.5 %.

-Score Ca coronario > 400 AU.

- DM 1 o 2:
> 60 años (varones) y
>65 años (mujeres).

PREVENCIÓN SECUNDARIA

- Enf. CV establecida.

MÉTODOS

POBLACIÓN ELEGIBLE

- Hipolipemiantes permitidos si necesario.:
  - Estatinas a dosis bajas.
  - Ezetimibe.
  - Niacina.
  - Fibratos.
  - Resinas secuestradoras acidos biliares.
  - Inhibidoes PCSK9.

STATIN INTOLERANCE CONFIRMATION FORM

1. **Patient Identification (Please Print or Type)**

Name:

Initials:

Screening Number:

Patient

My doctor has recommended that I take a medication (called a statin) to reduce the bad cholesterol (fats) in my blood. My doctor has told me that a statin would reduce my risk of a heart attack or stroke and the risk of death. However, I am not taking a statin (or I am taking a statin only at a very low dose) because of side effects. These side effects began or became worse when I was taking the statin and then went away or improved when I stopped taking it or decreased the dose. I can't tolerate these medications (called statins) even though I know they would reduce my risk of a heart attack or stroke or death. *My doctor has explained and I am aware that many patients who are unable to tolerate a single statin medication may also be able to tolerate a different statin or dose.*

Date **Signature of Patient**

Principal Investigator

For the purposes of the 1002-043 clinical study, in my opinion, this patient is unable to tolerate statin therapy (except possibly at very low average daily doses of atorvastatin <10 mg, fluvastatin <40 mg, lovastatin <20 mg, pravastatin <40 mg, pitavastatin <2 mg, rosuvastatin <5 mg or simvastatin <10 mg) based on my review of the medical and medication histories and discussion with the patient.

Date **Signature of Principal Investigator**

MÉTODOS

POBLACIÓN ELEGIBLE

CRITERIOS DE EXCLUSIÓN

- ✓ TG > 500 (sem 5).
- ✓ I. Renal: eGFR <30 ml/min/1.73 m2.
- ✓ ECV
- ✓ HbA1C >/ 10% sem 5.
- ✓ Hipotiroidismo no controlado
- ✓ Hepatopatía:
  GOT y GPT x 2 (sem 5). VHB +,VHC + (sem 4).
- ✓ Alteraciones GI que produzcan malabsorción
- ✓ Trast. hematológicos y coagulación. Hb< 10 (sem 5).
- ✓ CK x 3 (sem 5)
- ✓ Historia 2 años previos alcohol o drogas.
- ✓ Transfusión 30 días previos.
- ✓ Neoplasia activa o RT/QT en los 5 años previos.
- ✓ Embarazo, lactancia, deseo embarazo.

- 90 días previos:
  - AIT, ictus, IAM, revasc. coronaria o arterial periférica, endarterectomia o stent carotídeo.
- 90 días previos:
  - Arrítmica sintomática o inestable.
- MCP o DAI
  (sólo incluir si estabilidad 90 días previos)
- IC NYHA IV/IV.
- HTA no controlada (>/180/110)
- Revascularización coronaria programada
  (si posible inclusión 3 meses post-procedimiento)

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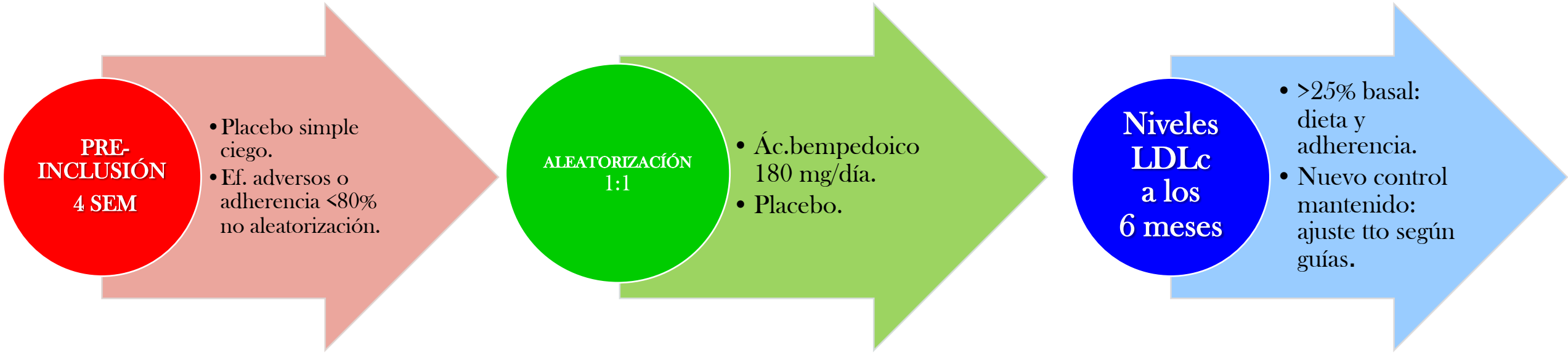
MÉTODOS

ALEATORIZACIÓN



MÉTODOS

OBJETIVOS

END POINT PRIMARIO

Evaluado hasta 1º evento CV el compuesto de:

- Muerte de causa CV.
- IAM no fatal.
- Ictus no fatal.
- Revascularización coronaria.

END POINT SECUNDARIO

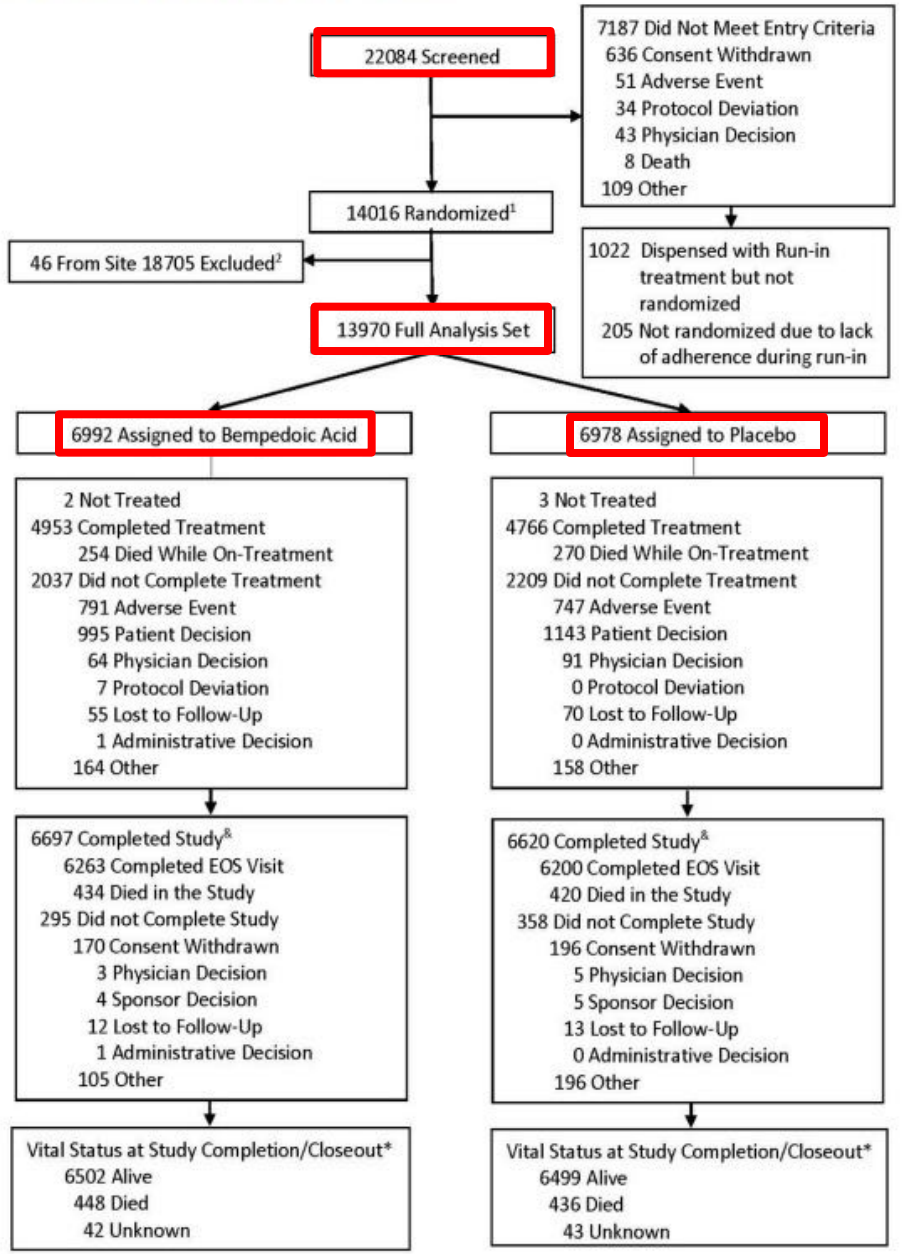
Evaluado hasta 1º evento CV:

- MACE: muerte causa CV, IAM no fatal, ictus no fatal.
- IAM fatal o no fatal.
- Revascularización coronaria.
- Ictus fatal o no fatal.
- Muerte de causa CV.
- Muerte por todas las causas.

RESULTADOS

- Diciembre 2016 a agosto 2019.
- Ánalisis por intención tratar (eficacia).

Figure S1 Flow of Patients through the Trial



[&]Complete assessment of the primary endpoint was available for 95.3% of patients

*Vital Status at Study Completion/Closeout was available for 99.4% of patients

RESULTADOS

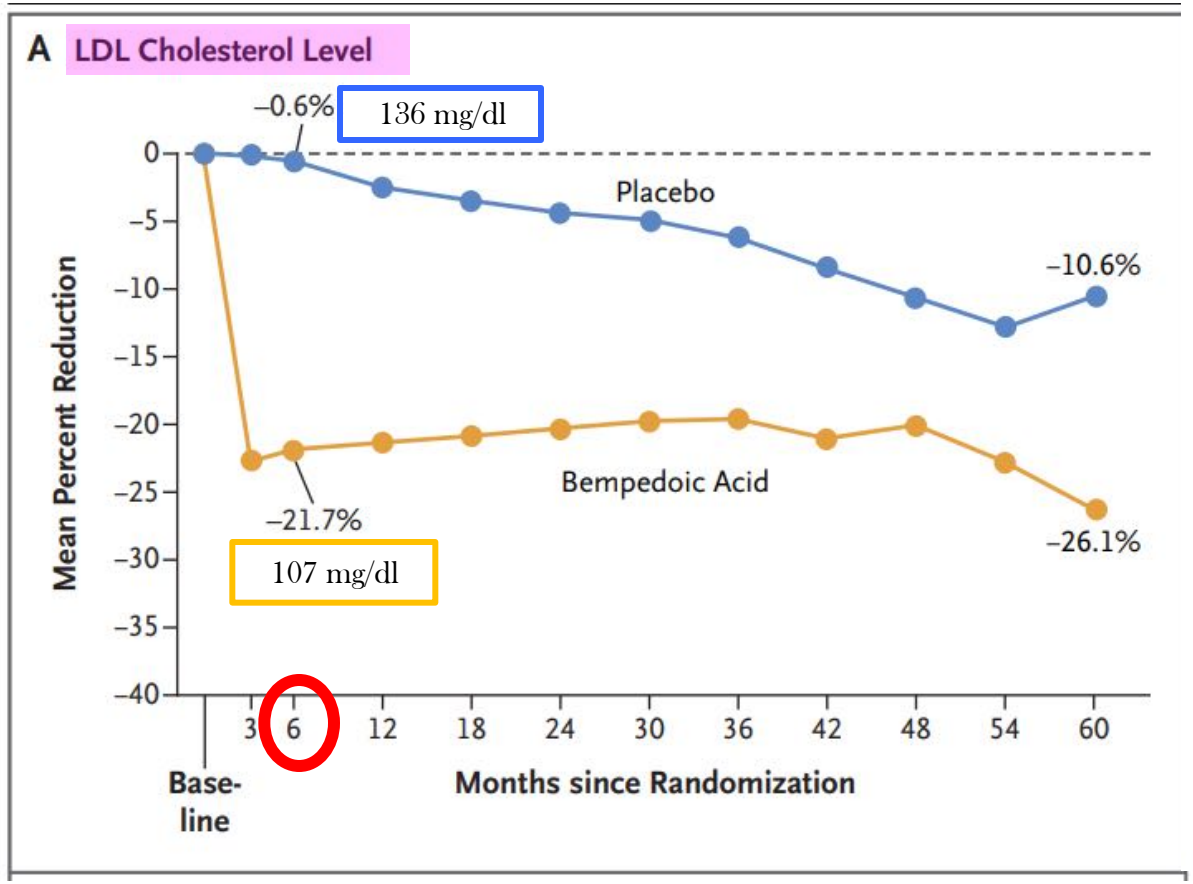
- Mediana de seguimiento: 40.6 meses.
- Interrupción precoz:
  - Ác bempedoico 2035 (29.1%) vs placebo 2212 (31.7%).
- Evaluación completa objetivo 1º: 95.3%.
- Estado vital al final: 99.4%.

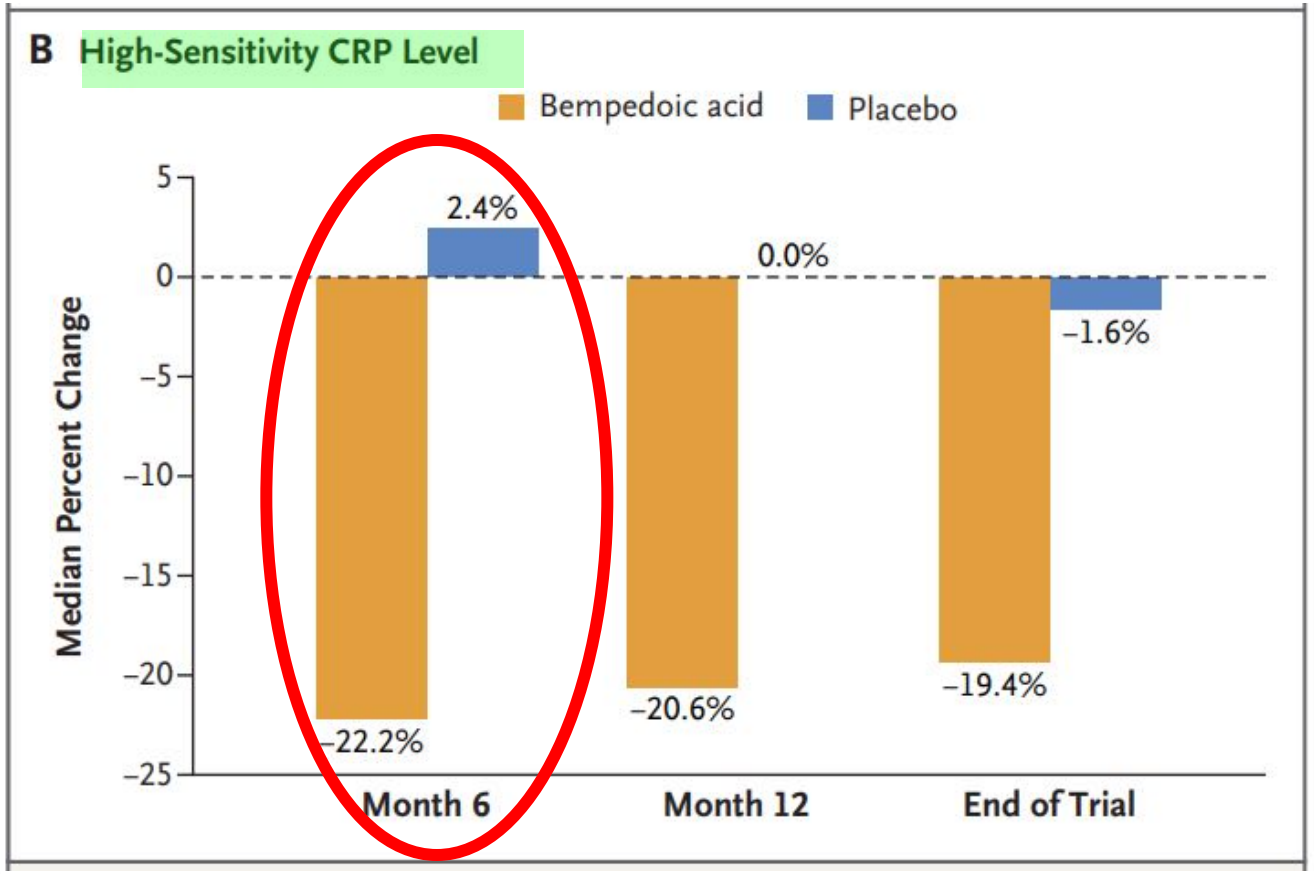
Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N=6992)	Placebo (N=6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Distribution — no. (%)		
<130 mg/dl	3074 (44.0)	3089 (44.3)
≥130 to <160 mg/dl	2213 (31.7)	2250 (32.2)
≥160 mg/dl	1705 (24.4)	1639 (23.5)
HDL cholesterol — mg/dl	49.6±13.3	49.4±13.3
Non-HDL cholesterol — mg/dl	173.8±39.5	173.9±40.2
Total cholesterol — mg/dl	223.5±40.6	223.3±41.1
Median triglycerides (IQR) — mg/dl	159.5 (118.0–216.5)	158.5 (118.0–215.0)
Median high-sensitivity CRP (IQR) — mg/liter	2.3 (1.2–4.5)	2.3 (1.2–4.5)
Estimated GFR — no. (%)		
≥90 ml/min/1.73 m^2	1216 (17.4)	1233 (17.7)
≥60 to <90 ml/min/1.73 m^2	4322 (61.8)	4282 (61.4)
≥30 to <60 ml/min/1.73 m^2	1437 (20.6)	1444 (20.7)
Cardiovascular risk category — no. (%)		
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

RESULTADOS

LDLc promedio 139 mg/dl





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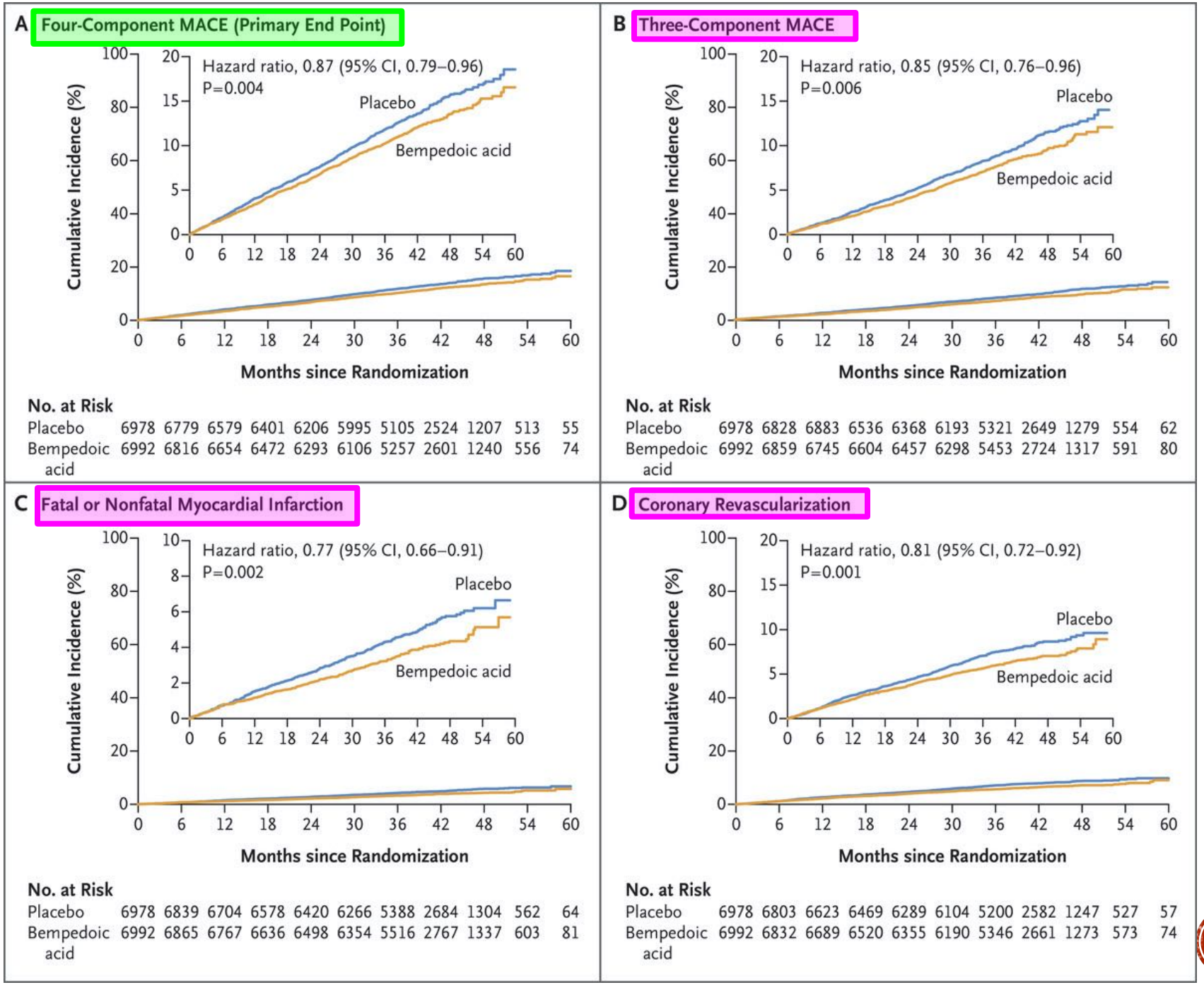
RESULTADOS

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

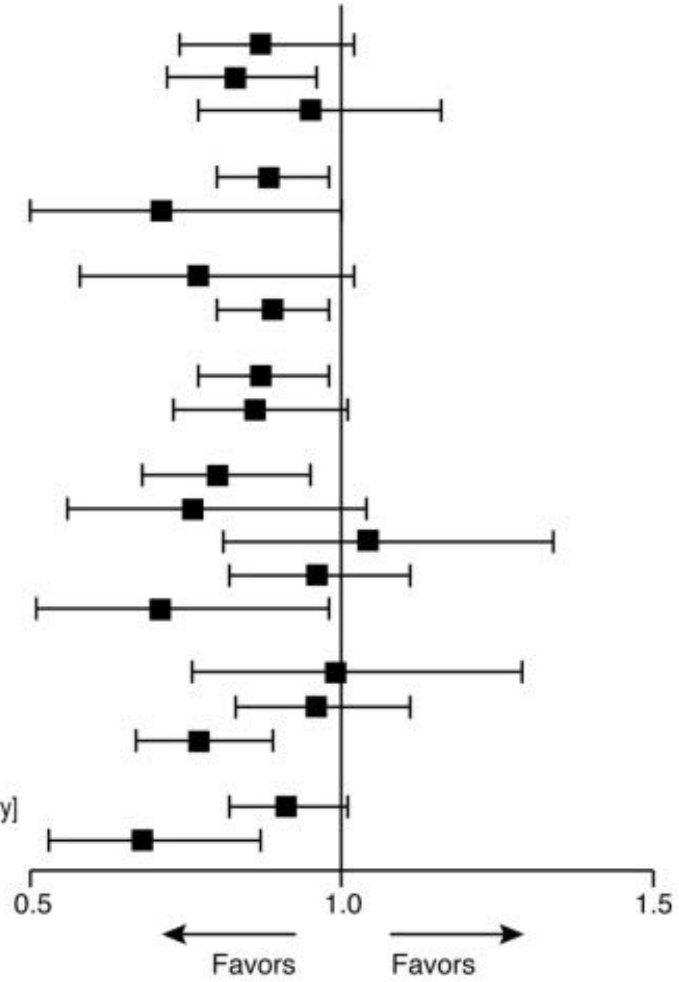
Outcome	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Difference (95% CI)*	P Value†
Primary efficacy end poin				
Four-component MACE — no. (%)‡	819 (11.7)	927 (13.3)	0.87 (0.79 to 0.96)	0.004
Key secondary efficacy end points				
Three-component MACE — no. (%)§	575 (8.2)	663 (9.5)	0.85 (0.76 to 0.96)	0.006
Fatal or nonfatal myocardial infarction — no. (%)	261 (3.7)	334 (4.8)	0.77 (0.66 to 0.91)	0.002
Coronary revascularization — no. (%)	435 (6.2)	529 (7.6)	0.81 (0.72 to 0.92)	0.001
Fatal or nonfatal stroke — no. (%)	135 (1.9)	158 (2.3)	0.85 (0.67 to 1.07)	0.16
Death from cardiovascular causes — no. (%)	269 (3.8)	257 (3.7)	1.04 (0.88 to 1.24)	
Death from any cause — no. (%)	434 (6.2)	420 (6.0)	1.03 (0.90 to 1.18)	
Additional secondary end points				
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization — no. (%)	962 (13.8)	1062 (15.2)	0.89 (0.82 to 0.97)	
Five-component MACE — no. (%)¶	831 (11.9)	952 (13.6)	0.86 (0.78 to 0.94)	
Hospitalization for unstable angina — no. (%)	91 (1.3)	137 (2.0)	0.66 (0.50 to 0.86)	
New-onset type 2 diabetes mellitus — no./total no. (%)‖	429/3848 (11.1)	433/3749 (11.5)	0.95 (0.83 to 1.09)	
Change from baseline in secondary lipid and biomarker efficacy end points				
Mean percent change in mean LDL cholesterol level at 6 mo (95% CI)**	−21.1 (−21.6 to −20.5)	−0.8 (−1.4 to −0.2)	−20.3 (−21.1 to −19.5)	
Median percent change in high-sensitivity CRP level at 6 mo (95% CI)	−22.2 (−23.5 to −20.8)	2.4 (0.0 to 4.2)	−21.6 (−23.7 to −19.6)	
Mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI)**††	−0.04 (−0.12 to 0.03)	−0.01 (−0.09 to 0.06)	−0.03 (−0.14 to 0.08)	

RESULTADOS


A Four-Component MACE (Primary End Point)
Hazard ratio, 0.87 (95% CI, 0.79–0.96)
P=0.004
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6779 6579 6401 6206 5995 5105 2524 1207 513 55
Bempedoic acid 6992 6816 6654 6472 6293 6106 5257 2601 1240 556 74
B Three-Component MACE
Hazard ratio, 0.85 (95% CI, 0.76–0.96)
P=0.006
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6828 6883 6536 6368 6193 5321 2649 1279 554 62
Bempedoic acid 6992 6859 6745 6604 6457 6298 5453 2724 1317 591 80
C Fatal or Nonfatal Myocardial Infarction
Hazard ratio, 0.77 (95% CI, 0.66–0.91)
P=0.002
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6839 6704 6578 6420 6266 5388 2684 1304 562 64
Bempedoic acid 6992 6865 6767 6636 6498 6354 5516 2767 1337 603 81
D Coronary Revascularization
Hazard ratio, 0.81 (95% CI, 0.72–0.92)
P=0.001
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6803 6623 6469 6289 6104 5200 2582 1247 527 57
Bempedoic acid 6992 6832 6689 6520 6355 6190 5346 2661 1273 573 74

RESULTADOS

Figure S3. Prespecified Subgroup Analyses for the Primary Endpoint



Endpoints	Hazard Ratio (95% CI)	Bempedoic Acid (N=6992)	Placebo (N=6978)	Interaction P value
Age category (years)				
<65	0.87 (0.74, 1.02)	275 (9.6)	321 (11.0)	
≥65 to < 75	0.83 (0.72, 0.96)	362 (11.8)	419 (13.8)	0.60
≥75	0.95 (0.77, 1.16)	182 (17.1)	187 (17.9)	
Race				
White	0.88 (0.80, 0.98)	766 (12.0)	846 (13.4)	0.21
Non-white	0.71 (0.50, 1.00)	53 (8.9)	81 (12.6)	
Ethnicity				
Hispanic or Latino	0.77 (0.58, 1.02)	85 (7.1)	106 (9.3)	0.35
Not Hispanic or Latino	0.89 (0.80, 0.98)	734 (12.7)	821 (14.1)	
Sex				
Male	0.87 (0.77, 0.98)	537 (14.8)	598 (16.6)	0.89
Female	0.86 (0.73, 1.01)	282 (8.4)	329 (9.7)	
Region				
North America (US and Canada)	0.80 (0.68, 0.95)	247 (16.4)	301 (19.9)	
Latin America	0.76 (0.56, 1.04)	70 (7.8)	89 (10.2)	
Western Europe	1.04 (0.81, 1.34)	123 (15.6)	122 (14.7)	0.17
Eastern Europe	0.96 (0.82, 1.11)	321 (9.4)	326 (9.9)	
Other (Rest of the World)	0.71 (0.51, 0.98)	58 (14.8)	89(19.7)	
Baseline BMI category (kg/m2)				
<25	0.99 (0.76, 1.29)	117 (10.9)	108 (10.7)	
≥25 to <30	0.96 (0.83, 1.11)	345 (12.2)	360 (12.5)	0.06
≥30	0.77 (0.67, 0.89)	357 (11.6)	459 (14.8)	
Baseline CVD risk category				
Secondary prevention [Documented CVD History]	0.91 (0.82, 1.01)	708 (14.5)	766 (15.7)	0.03
Primary prevention [At high risk for CVD]	0.68 (0.53, 0.87)	111 (5.3)	161 (7.6)	

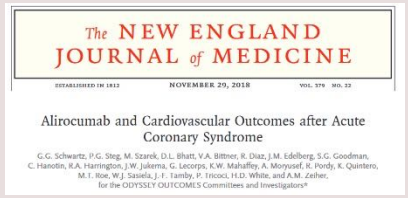
RESULTADOS

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.*

Event	Bempedoic Acid (N=7001)	Placebo (N=6964)
Any adverse event that started or worsened after the first dose of a trial agent — no. (%)	6040 (86.3)	5919 (85.0)
Serious adverse event that started or worsened after the first dose of a trial agent — no. (%)	1767 (25.2)	1733 (24.9)
Adverse event leading to discontinuation of the trial regimen — no. (%)	759 (10.8)	722 (10.4)
Prespecified adverse events of special interest		
Myalgia — no. (%)	393 (5.6)	471 (6.8)
Discontinuation of the trial regimen because of myalgia — no. (%)	124 (1.8)	129 (1.9)
New-onset diabetes in patients without diabetes at baseline — no./total no. (%)	621/3856 (16.1)	640/3740 (17.1)
New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)†	569/2918 (19.5)	586/2877 (20.4)
New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)†	52/938 (5.5)	54/863 (6.3)
Worsening hyperglycemia — no./total no. (%)‡	713/3145 (22.7)	746/3224 (23.1)
Hypoglycemia — no. (%)	304 (4.3)	267 (3.8)
Metabolic acidosis — no. (%)	13 (0.2)	11 (0.2)
Elevated hepatic-enzyme level — no. (%)	317 (4.5)	209 (3.0)
Renal impairment — no. (%)	802 (11.5)	599 (8.6)
Neurocognitive disorders — no. (%)	58 (0.8)	69 (1.0)
Atrial fibrillation — no. (%)	229 (3.3)	246 (3.5)
Adjudicated tendon rupture — no. (%)	86 (1.2)	66 (0.9)
Tendinopathies — no. (%)	118 (1.7)	128 (1.8)
Malignant conditions — no. (%)	321 (4.6)	341 (4.9)
Other adverse events — no. (%)		
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)
Laboratory results after 6 mo — mg/dl		
Change from baseline in uric acid level	0.76±1.2	−0.03±1.0
Change from baseline in creatinine level	0.05±0.2	0.01±0.2
Laboratory results after 12 mo		
Change from baseline in glycated hemoglobin level — %§	0.04±0.74	0.06±0.70
Abnormal enzyme level at any visit — no. (%)		
Creatine kinase level >5× ULN, single occurrence	45 (0.6)	40 (0.6)
Creatine kinase level >5× ULN, repeated and confirmed	8 (0.1)	8 (0.1)
Creatine kinase level >10× ULN, single occurrence	18 (0.3)	15 (0.2)
Creatine kinase level >10× ULN, repeated and confirmed	2 (<0.1)	4 (0.1)
Alanine aminotransferase level >3× ULN¶	83 (1.2)	53 (0.8)
Aspartate aminotransferase level >3× ULN¶	80 (1.1)	43 (0.6)

DISCUSIÓN

- ✓ Profármaco activación hepática ⇨ EVITA EFECTOS ADVERSOS MUSCULARES.
- ✓ **No** diabetogénicos.
- ✓ Mayor incidencia ⇨ hiperuricemia-gota, aumento Cr, elevación enz. hepáticas y colelitiasis (no previamente).
- ✓ Resultados similares en cuanto a **EVENTOS CV** a otros hipolipemiantes NO estatinas.
  - ❑ **Inhibidores PCSK9** ⇨ mayor reducción niveles LDLc pero reducción MACE similar.
  - ❑ **Ezetimibe** ⇨ menor reducción LDL con reducción **MACE similar.**


The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 29, 2018

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome


The NEW ENGLAND JOURNAL of MEDICINE

MAY 4, 2017

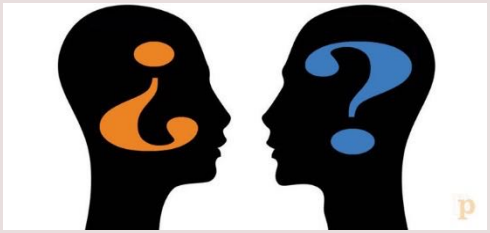
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease


The NEW ENGLAND JOURNAL of MEDICINE

JUNE 18, 2015

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

- ✓ Ningún hipolipemiante NO estatina ha demostrado **reducir mortalidad CV** (independiente).
  - ❑ Necesidad de terapias combinadas.
- ✓ **Mujeres 48%** (superior a otros ensayos) ⇨ HR evento **MACE similar hombres**
  - ❑ Análisis subgrupos (ajuste por multiplicidad...).
- ✓ Concepto "intolerancia a estatinas" controvertido ⇨ "EFECTO NOCEBO "



DISCUSIÓN

LIMITACIONES

- Se incluyen sólo pacientes intolerantes estatinas.

- LDLc más elevados.

-No estudiados efectos en poblaciones con niveles LDLc menores.

-No estudiado efecto pacientes con dosis convencionales estatinas.

✓En pacientes donde está indicada clínicamente la prevención primaria o secundaria de enfermedad cardiovascular y que sean "intolerantes" a dosis indicadas de estatinas, el ÁCIDO BEMPEDOICO es una alternativa, con reducción significativa de eventos CV tales como: muerte de causa CV, IAM no fatal, ictus no fatal y revascularización coronaria con una mediana de seguimiento de 40.6 meses.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Benefits of Bempedoic Acid — Clearer Now

John H. Alexander, M.D., M.H.S.

1

- Mayor eficacia ác bempedoico en **cohorte de prevención primaria** que cohorte de prevención secundaria ⇨ AZAR.
  - Mayor beneficio si administración fases precoces enfermedad ateroesclerótica.
  - Terapias concomitantes reducen beneficio del ácido bempedoico en la cohorte secundaria.

2

- NO efecto sobre la MORTALIDAD CV:
  - Terapia concomitante eficaz.
  - Periodo tratamiento y seguimiento cortos.
  - Ausencia real de efecto sobre mortalidad.
- Estatinas tampoco en ensayos indivuduales ⇨ **SÓLO en METANÁLISIS.**

ALGUNOS
FINALES
SON FELICES,
OTROS
NECESARIOS

MAL DÍA? - CAFÉ
BUEN DÍA? - CAFÉ
MONTÓN DE TRABAJO? - CAFÉ
PIEL RESECA? - CAFÉ

NADIE TE QUIERE? - CAFÉ
CAFÉ? - CAFÉ