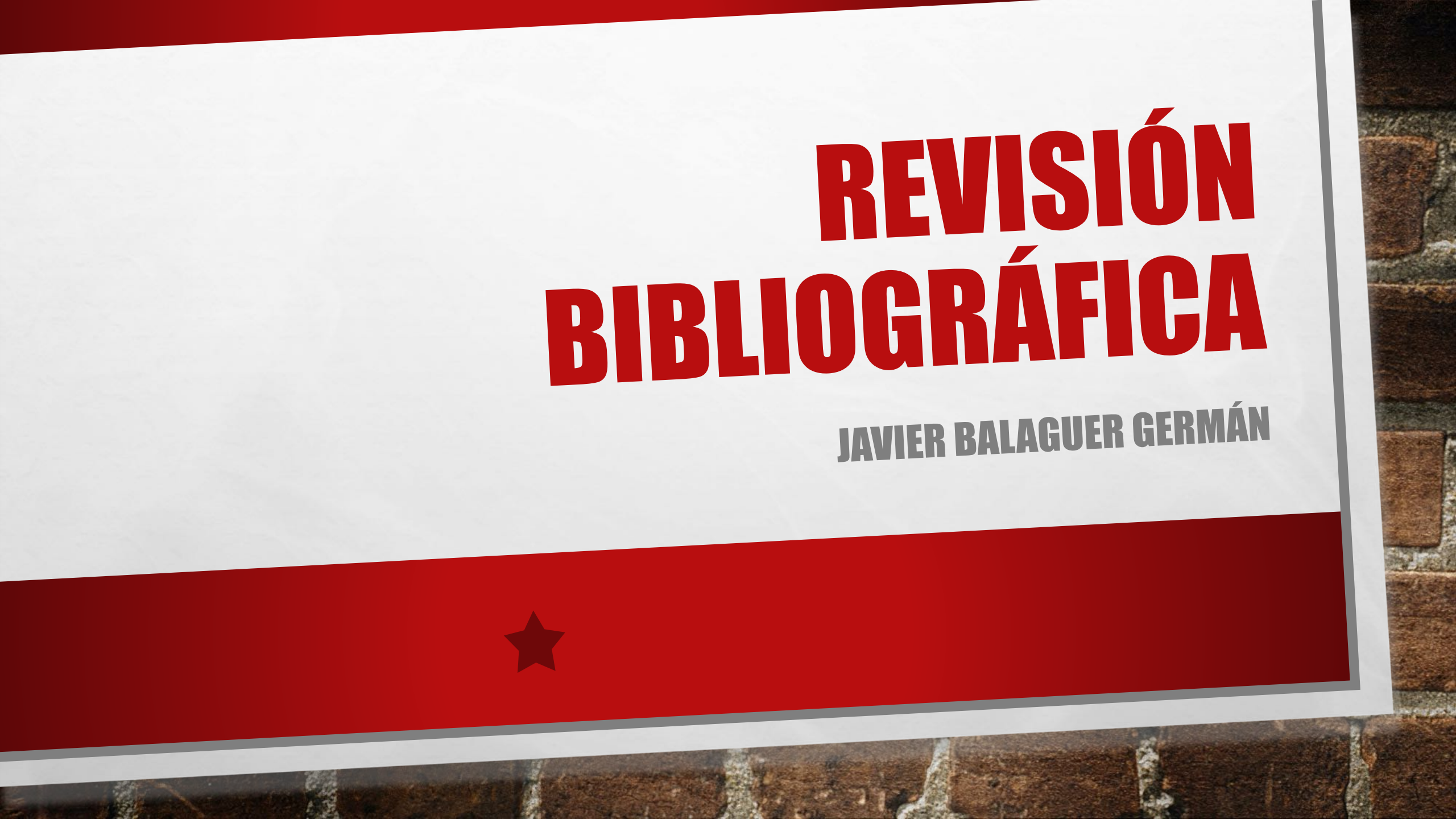
REVISIÓN BIBLIOGRÁFICA

JAVIER BALAGUER GERMÁN



The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

D. Mevorach, E. Anis, N. Cedar, M. Bromberg, E.J. Haas, E. Nadir, S. Olsha-Castell, D. Arad, T. Hasin, N. Levi, R. Asleh, O. Amir, K. Meir, D. Cohen, R. Dichtiar, D. Novick, Y. Hershkovitz, R. Dagan, I. Leitersdorf, R. Ben-Ami, I. Miskin, W. Saliba, K. Muhsen, Y. Levi, M.S. Green, L. Keinan-Boker, and S. Alroy-Preis

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 23, 2021 VOL. 385 NO. 13

Evidence of Artemisinin-Resistant Malaria in Africa

Betty Balikagala, M.D., Ph.D., Naoyuki Fukuda, M.D., D.T.M.H., Ph.D., Mie Ikeda, Ph.D., Osbert T. Katuro, B.Sc., Shin-Ichiro Tachibana, Ph.D., Masato Yamauchi, M.P.H., Ph.D., Walter Opio, M.D., Sakurako Emoto, M.D., Denis A. Anywar, M.Sc., Eisaku Kimura, M.D., Ph.D., Nirianne M.Q. Palacpac, Ph.D., Emmanuel I. Odongo-Aginya, Ph.D., Martin Ogwang, M.D., M.M.E.D., Toshihiro Horii, Ph.D., and Toshihiro Mita, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

D. Mevorach, E. Anis, N. Cedar, M. Bromberg, E.J. Haas, E. Nadir, S. Olsha-Castell, D. Arad, T. Hasin, N. Levi, R. Asleh, O. Amir, K. Meir, D. Cohen, R. Dichtiar, D. Novick, Y. Hershkovitz, R. Dagan, I. Leitersdorf, R. Ben-Ami, I. Miskin, W. Saliba, K. Muhsen, Y. Levi, M.S. Green, L. Keinan-Boker, and S. Alroy-Preis

INTRODUCCIÓN

Objetivo: presentar las características clínicas y epidemiológicas y los seguimiento de los casos de miocarditis que se diagnosticaron en la proximidad temporal de la vacunación y examinar una posible relación causal entre la vacuna y la entre la vacuna y la miocarditis.

20/Dic/2020

31/May/2021

5,12 millones de vacunados

MÉTODO

Clasificación Internacional de
Internacional de Enfermedades, 9ª Revisión (CIE-9)

Dic/2020 → **May/2021**

- **1º DOSIS→ 21 DÍAS**
- **2º DOSIS→ 30 DÍAS**

-Se separó entre sexos hombres y mujeres y según
de edad (16 a 19 años, 20 a 24 años, 25 a 29 años
29 años, 30 a 39 años, 40 a 49 años y 50 años o más).
años o más).
-Para evaluar la incidencia de la miocarditis
entre los receptores de la vacuna, se calcularon
las diferencias de riesgo, los cocientes observados/esperados y los
de tasas entre las personas vacunadas y las no vacunadas.

RESULTADOS

Table 1. Reported Myocarditis Cases, According to Timing of First or Second Vaccine Dose.*

Timing	First Vaccine Dose			Second Vaccine Dose			Both Doses
	No. of Vaccinations	Myocarditis Cases	Males/ Females	No. of Vaccinations	Myocarditis Cases	Males/ Females	Myocarditis Cases
Six-month study period	5,442,696	19	17/2	5,125,635	117	101/16	136
December 2020	987,013	0	0/0	0	0	0/0	0
January 2021	2,109,854	4	3/1	1,844,896	13	12/1	17
February 2021	1,613,909	6	5/1	1,546,184	47	41/6	53
March 2021	528,069	7	7/0	1,397,609	44	38/6	51
April 2021	152,765	1	1/0	253,701	13	10/3	14
May 2021	51,086	1	1/0	83,245	0	0	1

* Data are from medical records, including clinical and laboratory data and discharge summaries, from the Ministry of Health database from December 2020 through May 2021, according to the codes for myocarditis used in the *International Classification of Diseases, 9th Revision*. Cases of myocarditis were reported within 21 days after the first dose of vaccine and 30 days after the second dose. All cases were clinically reviewed, and only definite or probable cases are shown.

RESULTADOS

Table 2. Classification of Myocarditis Cases Reported to the Ministry of Health.*

Timing of Myocarditis Diagnosis	Brighton Collaboration Classification of Myocarditis					
	Level 1	Level 2	Level 3	Level 4	Level 5	All Levels
	number of cases					
All cases	118	153	3	9	21	304
Vaccinated persons						
≤21 days after first dose and 30 days after second dose	55	81	1	5	9	151
>21 days after first dose and 30 days after second dose	15	23	0	2	5	45
Unvaccinated persons	48	49	2	2	7	108

* In the Brighton Collaboration classification system for the diagnosis of myocarditis, level 1 indicates definite, level 2 probable, level 3 possible, level 4 insufficient data, and level 5 ruled out. Included are data for persons who had a delayed second dose of vaccine and who received a diagnosis of myocarditis 22 days or longer after the first dose and those in whom myocarditis developed more than 30 days after the second dose, so the diagnosis was not considered to have been made in temporal proximity to vaccination.

RESULTADOS

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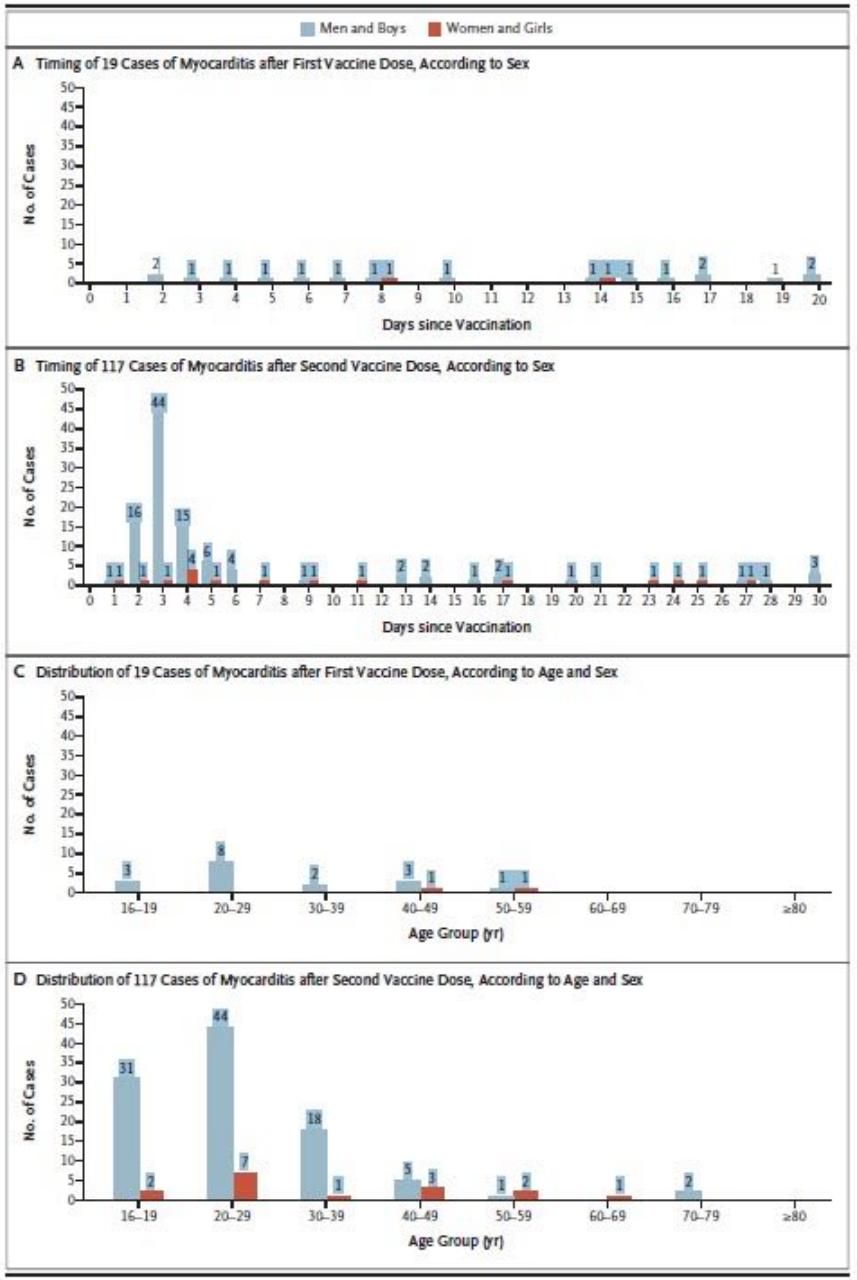
RESULTADOS


Men and Boys
Women and Girls
A Timing of 19 Cases of Myocarditis after First Vaccine Dose, According to Sex
No. of Cases
Days since Vaccination
B Timing of 117 Cases of Myocarditis after Second Vaccine Dose, According to Sex
No. of Cases
Days since Vaccination
C Distribution of 19 Cases of Myocarditis after First Vaccine Dose, According to Age and Sex
No. of Cases
16–19
20–29
30–39
40–49
50–59
60–69
70–79
≥80
Age Group (yr)
D Distribution of 117 Cases of Myocarditis after Second Vaccine Dose, According to Age and Sex
No. of Cases
16–19
20–29
30–39
40–49
50–59
60–69
70–79
≥80
Age Group (yr)

RESULTADOS

Table 3. Risk of Myocarditis within 21 Days after the First or Second Dose of Vaccine, According to Age and Sex.*

Age and Sex	First Dose			Second Dose			Risk Difference (95% CI)
	Recipients	Cases	Risk per 100,000 Persons	Recipients	Cases	Risk per 100,000 Persons	
	number			*number*			*no./100,000 persons*
Male recipients							
All ages	2,668,894	17	0.64	2,507,210	96	3.83	3.19 (2.37 to 4.02)
16–19 yr	224,518	3	1.34	199,115	30	15.07	13.73 (8.11 to 19.46)
20–24 yr	261,741	5	1.91	239,396	26	10.86	8.95 (4.42 to 13.55)
25–29 yr	246,638	3	1.22	228,988	16	6.99	5.77 (2.02 to 9.58)
30–39 yr	491,126	2	0.41	461,044	17	3.69	3.28 (1.41 to 5.18)
40–49 yr	458,268	3	0.65	433,069	5	1.15	0.50 (–0.82 to 1.84)
≥50 yr	986,603	1	0.10	945,598	2	0.21	0.11 (–0.29 to 0.52)
Female recipients							
All ages	2,773,802	2	0.07	2,618,425	12	0.46	0.39 (0.10 to 0.68)
16–19 yr	219,460	0	0	199,706	2	1.00	1.00 (–0.63 to 2.72)
20–24 yr	250,556	0	0	231,960	5	2.16	2.16 (0.13 to 4.24)
25–29 yr	235,575	0	0	219,113	0	0	0 (–0.83 to 0.89)
30–39 yr	481,045	0	0	451,791	1	0.22	0.22 (–0.37 to 0.84)
40–49 yr	472,083	1	0.21	444,916	2	0.45	0.24 (–0.61 to 1.11)
≥50 yr	1,115,083	1	0.09	1,070,939	2	0.19	0.10 (–0.26 to 0.46)

* Among vaccine recipients of all ages and both sexes, the overall difference in the incidence of myocarditis after the second dose as compared with the incidence after the first dose was 1.76 (95% confidence interval [CI], 1.33 to 2.19). The widths of the confidence intervals have not been adjusted for multiple testing.

DISCUSIÓN

- EL RIESGO DE MIOCARDITIS SE DEBIÓ PRINCIPALMENTE AL AUMENTO DE LA INCIDENCIA DESPUÉS DE LA SEGUNDA DOSIS DE VACUNA Y EN LOS RECEPTORES MASCULINOS JÓVENES.

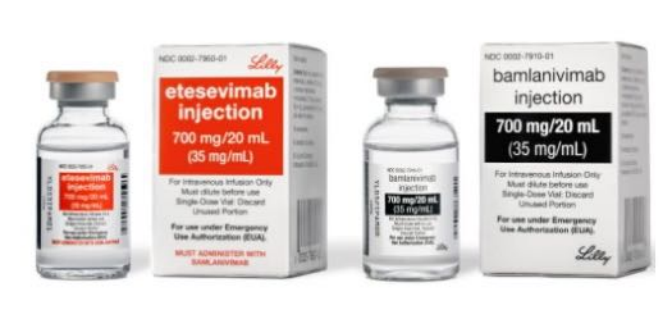
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

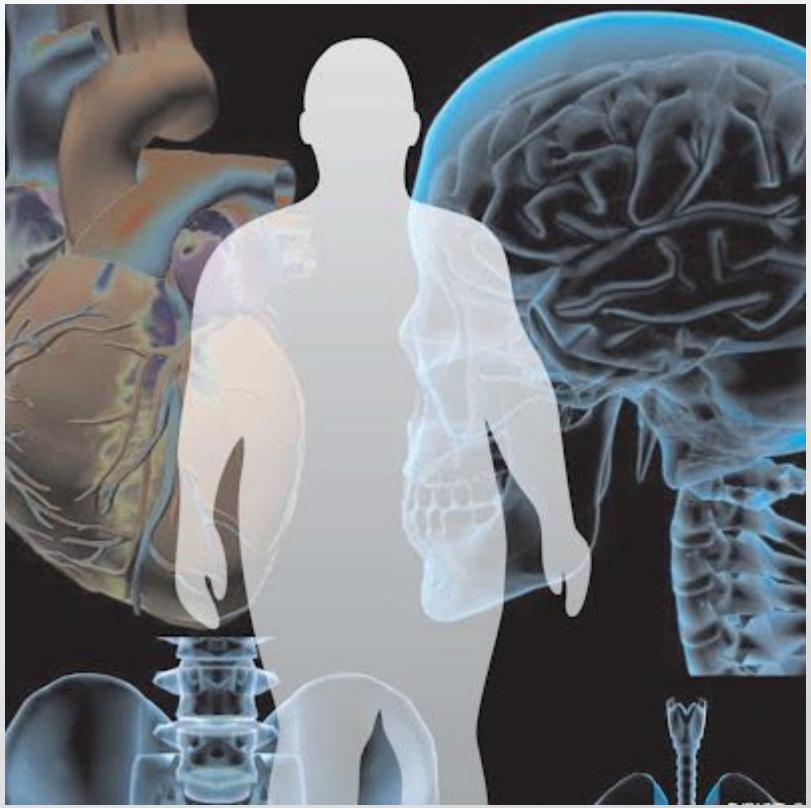
Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19

M. Dougan, A. Nirula, M. Azizad, B. Mocherla, R.L. Gottlieb, P. Chen, C. Hebert, R. Perry, J. Boscia, B. Heller, J. Morris, C. Crystal, A. Igbinadolor, G. Huhn, J. Cardona, I. Shawa, P. Kumar, A.C. Adams, J. Van Naarden, K.L. Custer, M. Durante, G. Oakley, A.E. Schade, T.R. Holzer, P.J. Ebert, R.E. Higgs, N.L. Kallewaard, J. Sabo, D.R. Patel, M.C. Dabora, P. Klekotka, L. Shen, and D.M. Skovronsky, for the BLAZE-1 Investigators*

INTRODUCCIÓN



Objetivo: informar de los resultados de la última parte del del ensayo de fase 3 BLAZE-1 en el que una cohorte de adolescentes (≥12 años de edad) y adultos ambulatorios con Covid-19 leve o moderada y con alto riesgo de riesgo de padecer una enfermedad grave recibieron bamlanivimab-etesevimab o placebo.



MÉTODO

- EN ESTE ENSAYO EN CURSO DE FASE 2-3,
- ALEATORIZADO, DOBLE CIEGO
- CONTROLADO CON PLACEBO Y DE DOSIS ÚNICA
- TODOS LOS PACIENTES HABÍAN RECIENTEMENTE UN DIAGNÓSTICO DE ENFERMEDAD LEVE O MODERADA.
- UNA ÚNICA DOSIS DE 2800 MG DE BAMLANIVIMAB Y 2800 MG DE ETESEVIMAB O PLACEBO DURANTE UN PERÍODO DE 1 HORA.

Factores de riesgo en función de la edad.

MÉTODO

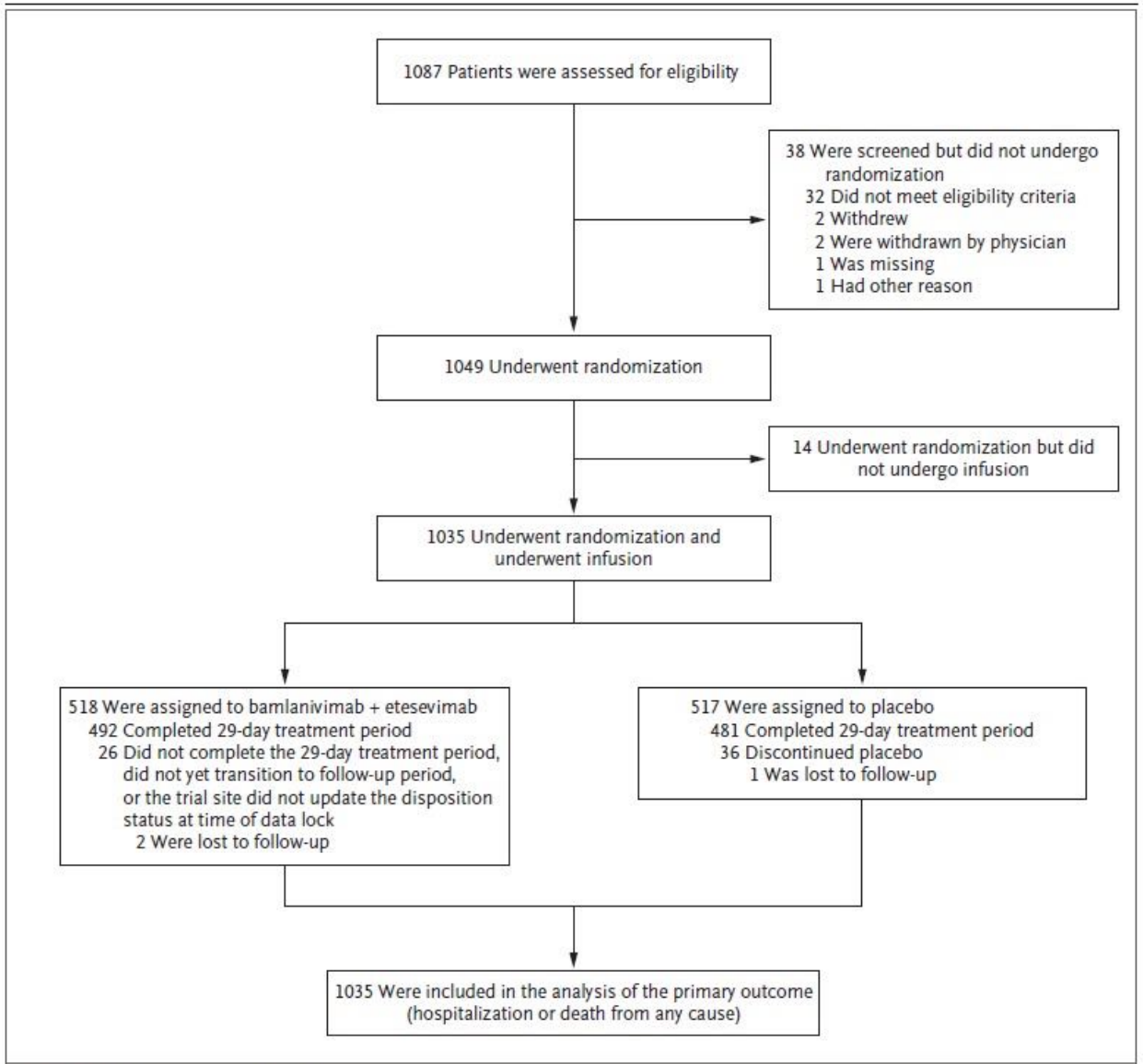


Figure 1. Enrollment and Trial Design.

CDC denotes Centers for Disease Control and Prevention, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

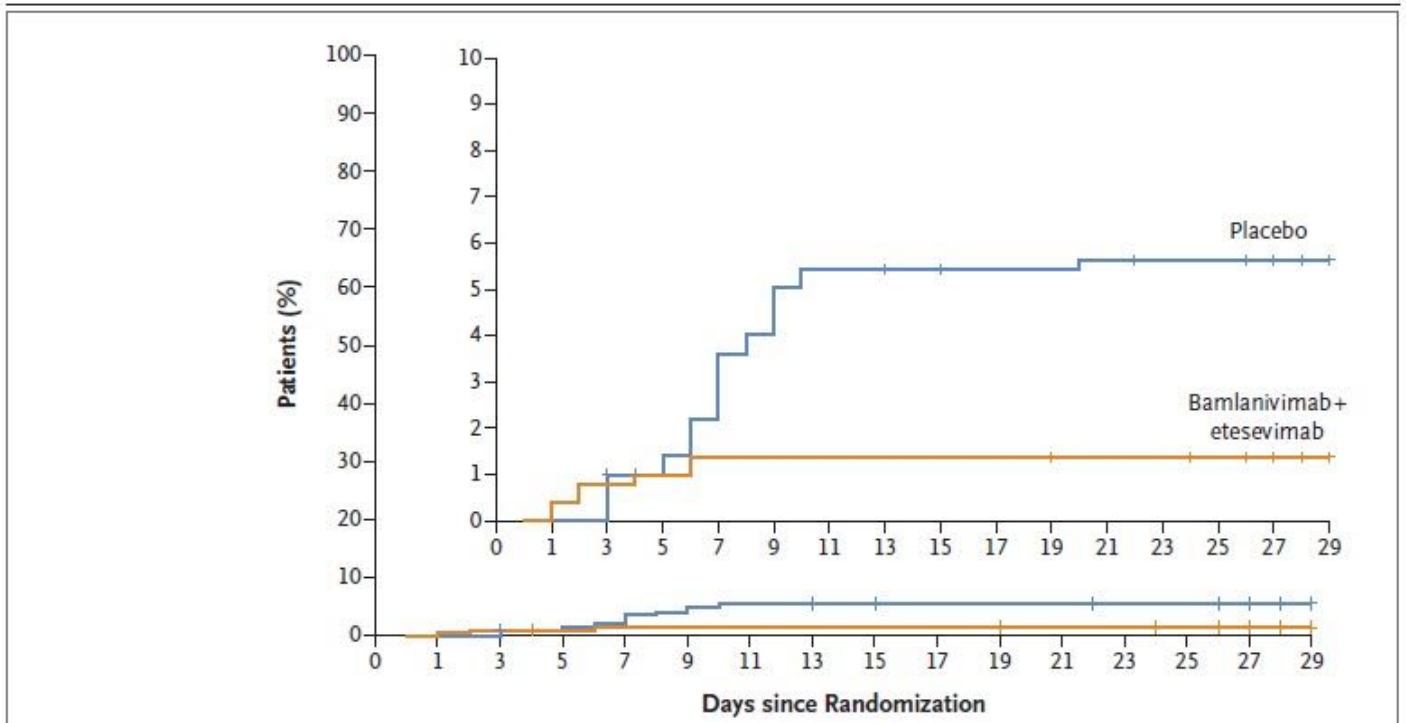
RESULTADOS

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Bamlanivimab plus Etesevimab (N=518)	Placebo (N=517)	Total (N=1035)
Age			
Mean ±SD — yr	54.3±17.1	53.3±16.4	53.8±16.8
65 yr or older — no. (%)	168 (32.4)	155 (30.0)	323 (31.2)
Race or ethnic group — no./total no. (%)†			
American Indian or Alaska Native	2/512 (0.4)	1/513 (0.2)	3/1025 (0.3)
Asian	16/512 (3.1)	22/513 (4.3)	38/1025 (3.7)
Black	44/512 (8.6)	39/513 (7.6)	83/1025 (8.1)
Native Hawaiian or other Pacific Islander	0	2/513 (0.4)	2/1025 (0.2)
White	449/512 (87.7)	447/513 (87.1)	896/1025 (87.4)
Multiple races or ethnic groups	1/512 (0.2)	2/513 (0.4)	3/1025 (0.3)
Missing data	6	4	10
Hispanic or Latinx	149/517 (28.8)	155/516 (30.0)	304/1033 (29.4)
Median body-mass index‡	34.14	33.90	34.09
Peripheral oxygen saturation — no./total no. (%)			
<96%	90/516 (17.4)	106/514 (20.6)	196/1030 (19.0)
≥96%	426/516 (82.6)	408/514 (79.4)	834/1030 (81.0)
Risk of severe Covid-19 — no./total no. (%)			
High	493/518 (95.2)	490/517 (94.8)	983/1035 (95.0)
Low	25/518 (4.8)	27/517 (5.2)	52/1035 (5.0)
Disease status — no. (%)			
Mild Covid-19	397 (76.6)	403 (77.9)	800 (77.3)
Moderate Covid-19	121 (23.4)	114 (22.1)	235 (22.7)
Median days from symptom onset to randomization — no. (range)	4 (0–29)	4 (0–13)	40 (0–29)
Mean viral load — Ct value§	23.98	23.97	23.97

* Covid-19 denotes coronavirus disease 2019.
† Race or ethnic group was reported by the patients, who could choose more than one category.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Ct denotes the cycle threshold on the reverse-transcriptase–polymerase-chain-reaction assay.

RESULTADOS



No. at Risk															
Placebo	499	493	490	479	472	470	469	468	468	468	467	465	465	436	159
Bamlanivimab+etesevimab	506	504	502	500	500	500	500	500	500	499	499	499	498	459	149
No. of Events															
Placebo	5	2	11	7	2	0	0	0	0	1	0	0	0	0	0
Bamlanivimab+etesevimab	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0

Figure 2. Kaplan–Meier Estimate of the Time to Hospitalization among High-Risk Patients Who Received Bamlanivimab–Etesevimab or Placebo.

The inset shows the same data on an enlarged y axis. Tick marks indicate censored data.

RESULTADOS

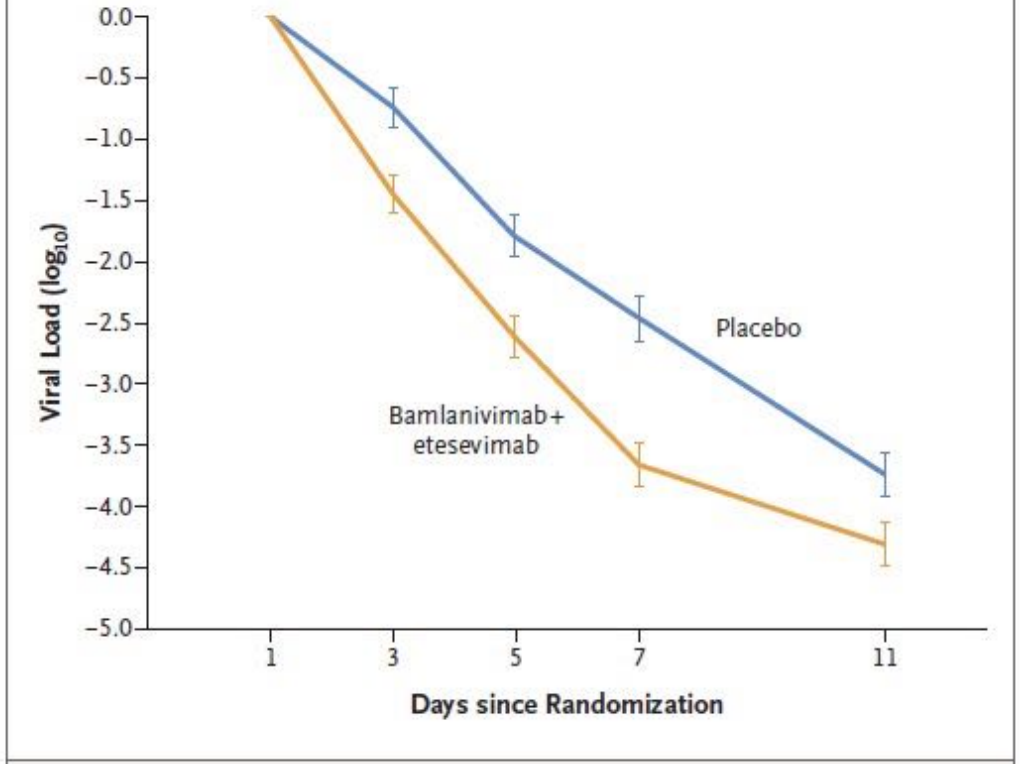


Figure 3. Effect of Bamlanivimab–Etesevimab on Viral Load (Days 1–11).
The mean change in the viral load from baseline to day 11 after the initiation of bamlanivimab–etesevimab or placebo is shown. The viral load was calculated from the cycle-threshold value on reverse-transcriptase–polymerase-chain-reaction assay. The error bars indicate 95% confidence intervals.

RESULTADOS

Table 2. Adverse Events.

Adverse Event	Bamlanivimab plus Etesevimab (N=518)	Placebo (N=517)	Total (N=1035)
	number of patients (percent)		
Serious adverse events	7 (1.4)	5 (1.0)	12 (1.2)
Adverse events	69 (13.3)	60 (11.6)	129 (12.5)
Mild	37 (7.1)	35 (6.8)	72 (7.0)
Moderate	24 (4.6)	20 (3.9)	44 (4.3)
Severe	7 (1.4)	5 (1.0)	12 (1.2)
Missing data	1 (0.2)	0	1 (0.1)
Death from adverse event	0	1 (0.2)	1 (0.1)
Most common adverse events according to preferred term			
Nausea	5 (1.0)	4 (0.8)	9 (0.9)
Rash	6 (1.2)	3 (0.6)	9 (0.9)
Dizziness	4 (0.8)	3 (0.6)	7 (0.7)
Diarrhea	2 (0.4)	2 (0.4)	4 (0.4)
Hypertension	2 (0.4)	2 (0.4)	4 (0.4)
Vaginal infection*	1/279 (0.4)	1/259 (0.4)	2/538 (0.4)
Gastroesophageal reflux disease	3 (0.6)	0	3 (0.3)
Pruritus	3 (0.6)	0	3 (0.3)
Urinary tract infection	3 (0.6)	0	3 (0.3)
Urticaria	2 (0.4)	1 (0.2)	3 (0.3)
Vomiting	2 (0.4)	1 (0.2)	3 (0.3)
Abdominal pain	1 (0.2)	1 (0.2)	2 (0.2)
Increased blood level of creatine kinase	1 (0.2)	1 (0.2)	2 (0.2)
Covid-19	0	2 (0.4)	2 (0.2)
Constipation	1 (0.2)	1 (0.2)	2 (0.2)
Dehydration	1 (0.2)	1 (0.2)	2 (0.2)
Dysgeusia	2 (0.4)	0	2 (0.2)
Dyspepsia	2 (0.4)	0	2 (0.2)
Fungal infection	0	2 (0.4)	2 (0.2)
Headache	1 (0.2)	1 (0.2)	2 (0.2)

* The numbers shown for this event are the numbers of adolescent girls or women who had the event and the total numbers of adolescent girls or women in the two groups in the trial.

DISCUSIÓN

- INDICARON LA EFICACIA DE LA INTERVENCIÓN TEMPRANA CON BAMLANIVIMAB MÁS ETESEVIMAB PARA REDUCIR LA INCIDENCIA DE HOSPITALIZACIÓN RELACIONADAS CON COVID-19. ENTRE LOS PACIENTES QUE RECIBIERON BAMLANIVIMAB MÁS ETESEVIMAB.
- SIN OBJETIVARSE FALLECIMIENTOS POR COVID EN EL GRUPO DEL TRATAMIENTO MONOCLONAL
- LIMITACIONES:
  - SÓLO EL 12,6% DE LOS PACIENTES SE IDENTIFICARON COMO NO BLANCOS
  - SÓLO EL 1,1% DE LOS PACIENTES TENÍAN ENTRE 12 Y 17 AÑOS DE EDAD.

The NEW ENGLAND JOURNAL of MEDICINE

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Evidence of Artemisinin-Resistant Malaria in Africa

Betty Balikagala, M.D., Ph.D., Naoyuki Fukuda, M.D., D.T.M.H., Ph.D., Mie Ikeda, Ph.D., Osbert T. Katuro, B.Sc., Shin-Ichiro Tachibana, Ph.D., Masato Yamauchi, M.P.H., Ph.D., Walter Opio, M.D., Sakurako Emoto, M.D., Denis A. Anywar, M.Sc., Eisaku Kimura, M.D., Ph.D., Nirianne M.Q. Palacpac, Ph.D., Emmanuel I. Odongo-Aginya, Ph.D., Martin Ogwang, M.D., M.M.E.D., Toshihiro Horii, Ph.D., and Toshihiro Mita, M.D., Ph.D.

INTRODUCCIÓN

- EN 2019, SE ESTIMA QUE 229 MILLONES DE CASOS DE MALARIA QUE HAN PROVOCADO 409.000 MUERTES.
- GEN KELCH (M476I, P553L, R561H Y P574L)→12,8%
- DOS MUTACIONES DE KELCH13, A675V Y C469Y, FUERON PARTICULARMENTE SEÑALADAS COMO CANDIDATAS DE RESISTENCIA A LA ARTEMISININA EN ESTUDIOS RECIENTES IN VITRO

MÉTODO

- ESTE ESTUDIO SE LLEVÓ A CABO DESDE 2015 HASTA 2019 EN EL HOSPITAL ST. MARY'S LACOR DE GULU, NORTE DE UGANDA
- CRITERIOS DE INCLUSIÓN:
  - NO ESTABAN LIMITADOS A RANGOS DE EDAD
  - ESTABAN INFECTADOS P. FALCIPARUM
  - PARASITEMIA DE MÁS DE 10.000 ORGANISMOS POR MICROLITRO.
- CRITERIOS DE EXCLUSIÓN:
  - SI HABÍAN RECIBIDO UN FÁRMACO ANTIPALÚDICO EN LAS 2 SEMANAS ANTES DE LA INSCRIPCIÓN
  - SI TENÍAN UNA ENFERMEDAD CRÓNICA COEXISTENTE.

MÉTODO

- SE ADMINISTRÓ INTRAVENOSA A UNA DOSIS DE 3 MG/KG (EN PACIENTES QUE PESABAN <20 KG) O 2,4 MG/KG (EN LOS QUE PESABAN ≥20 KG) A LAS 0, 12 Y 24 HORAS, SEGUIDO DE UN TRATAMIENTO UN CICLO ESTÁNDAR DE 3 DÍAS DE ARTEMÉTER-LUMEFANTRINA.
- SE RECOGIERON FROTIS DE SANGRE FINA Y GRUESA POR DUPLICADO A LAS 0, 4 Y 6 HORAS Y DESPUÉS A 6 HORAS HASTA QUE SE OBTUVIERON DOS FROTIS SANGUÍNEOS NEGATIVOS CONSECUTIVOS. SI SE OBSERVABAN PARÁSITOS DESPUÉS DE LAS TRES DOSIS INICIALES, SE ADMINISTRARON DOSIS ADICIONALES DE ARTESUNATO INTRAVENOSO CADA 24 HORAS HASTA QUE SE OBSERVARA LA ELIMINACIÓN DE LOS PARÁSITOS.
- SI LA DIFERENCIA EN LA VIDA MEDIA DE ELIMINACIÓN DETERMINADA POR DOS EXAMINADORES ERA SUPERIOR A 1 HORA, UN TERCER EXAMINADOR TAMBIÉN PROPORCIONÓ UNA MEDIDA→ ESTIMADOR DE ELIMINACIÓN DEL PARÁSITO DESARROLLADO POR DESARROLLADO POR LA RED MUNDIAL DE RESISTENCIA ANTIMALÁRICA
- UNA SEMIVIDA DE ELIMINACIÓN MEDIA DE MÁS DE MÁS DE 5 HORAS SE CONSIDERÓ QUE INDICABA UNA RESISTENCIA IN VIVO A LA ARTEMISININA RESISTENCIA A LA ARTEMISININA.

MÉTODO

- EL ADN DEL PARÁSITO SE EXTRAJO MEDIANTE MEDIANTE UN MINI KIT DE ADN QIAAMP (QIAGEN).
  - KELCH13

- ESTUDIO ESTADÍSTICO:
  - PREVALENCIA DEL PARÁSITO PARÁSITOS MEDIANTE LA PRUEBA DE COCHRAN-ARMITAGE.
  - EL COEFICIENTE DE CORRELACIÓN DE SPEARMAN SE UTILIZÓ PARA EVALUAR LA CORRELACIÓN ENTRE LA EFICACIA IN VIVO Y EX VIVO.
  - PARA ESTUDIAR LA ASOCIACIÓN ENTRE LA EFICACIA DEL DE LOS FÁRMACOS Y LOS GENOTIPOS, SE UTILIZÓ LA PRUEBA DE SUMA DE RANGOS DE WILCOXON DE WILCOXON, LA PRUEBA EXACTA DE FISHER Y EL ANÁLISIS DE REGRESIÓN DE REGRESIÓN MÚLTIPLE.
  - LAS COMPARACIONES MÚLTIPLES SE AJUSTARON CON CON EL MÉTODO DE BONFERRONI.

RESULTADOS

Table 1. Characteristics of the Patients with Measured Parasite Clearance Half-Life, According to Study Year.*

Characteristic	2017 (N=87)	2018 (N=60)	2019 (N=93)	Total (N=240)
Median age (IQR) — yr	2.5 (1.6–4.0)	2.8 (1.8–4.4)	2.7 (1.5–4.0)	2.6 (1.6–4.0)
Female sex — no. (%)	42 (48)	29 (48)	36 (39)	107 (45)
Median temperature (IQR) — °C	38.6 (37.7–39.4)	38.5 (37.9–39.2)	38.4 (37.8–39.5)	38.6 (37.8–39.3)
Laboratory findings				
Median hemoglobin (IQR) — g/dl	12.8 (10.9–14.3)	10.5 (9.3–11.5)	9.4 (8.4–10.7)	10.6 (9.2–12.3)
Median parasite density (IQR) — mm^3	138,000 (73,000–228,000)	91,800 (67,000–127,000)	128,700 (84,600–186,000)	117,000 (70,000–189,000)
Gametocytemia — no. (%)	2 (2)	1 (2)	4 (4)	7 (3)
Median parasite clearance half-life (IQR) — hr	2.00 (1.62–2.42)	1.71 (1.53–2.14)	1.77 (1.48–2.22)	1.85 (1.52–2.32)
Parasite clearance half-life of >5 hr — no. (%)	4 (5)	4 (7)	6 (6)	14 (6)
kelch13 genotype — no. (%)†				
C469Y	0	1 (2)	4 (4)	5 (2)
A675V	8 (9)	8 (13)	11 (12)	27 (11)
Other mutation	0	2 (3)	4 (4)	6 (2)
Wild type	79 (91)	49 (82)	74 (80)	202 (84)

* The parasite clearance half-life was successfully determined in 240 of the study patients. The prevalence of in vivo resistance (defined as a parasite clearance half-life of >5 hours) increased slightly during the study period, but the difference with the prevalence at baseline was not significant (P=0.60). IQR denotes interquartile range.

† During the study period, mixed alleles were present in 1 patient with the C469Y allele, in 10 patients with the A675V allele, and in 3 patients with other mutations.

RESULTADOS

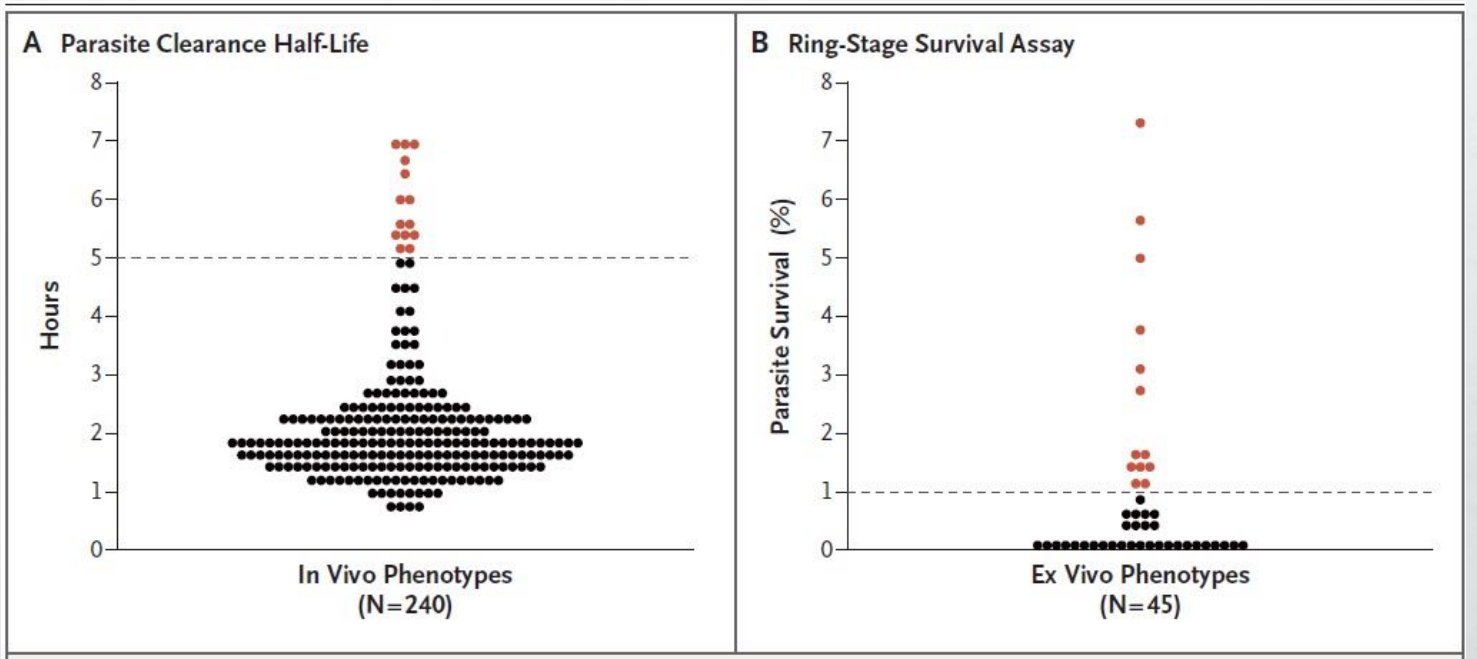

Figure 2. Demonstration of Artemisinin Resistance.

Panel A shows the parasite clearance half-life in 240 of the study patients for whom data were available. Parasites were rapidly cleared in most patients, with a median half-life of 1.9 hours (interquartile range, 1.5 to 2.3). However, 14 patients (5.8%) had evidence of slow parasite clearance (defined as a half-life of >5 hours) and were considered to have in vivo artemisinin resistance (indicated in red). Panel B shows the results of ex vivo ring-stage survival assays in 45 of 113 patients who were evaluated. Among these patients, 13 (29%) had parasite survival of more than 1% (indicated in red). Each data point represents a single patient. The ex vivo survival rate of parasites correlated with the in vivo clearance half-life (correlation coefficient, 0.29).

RESULTADOS

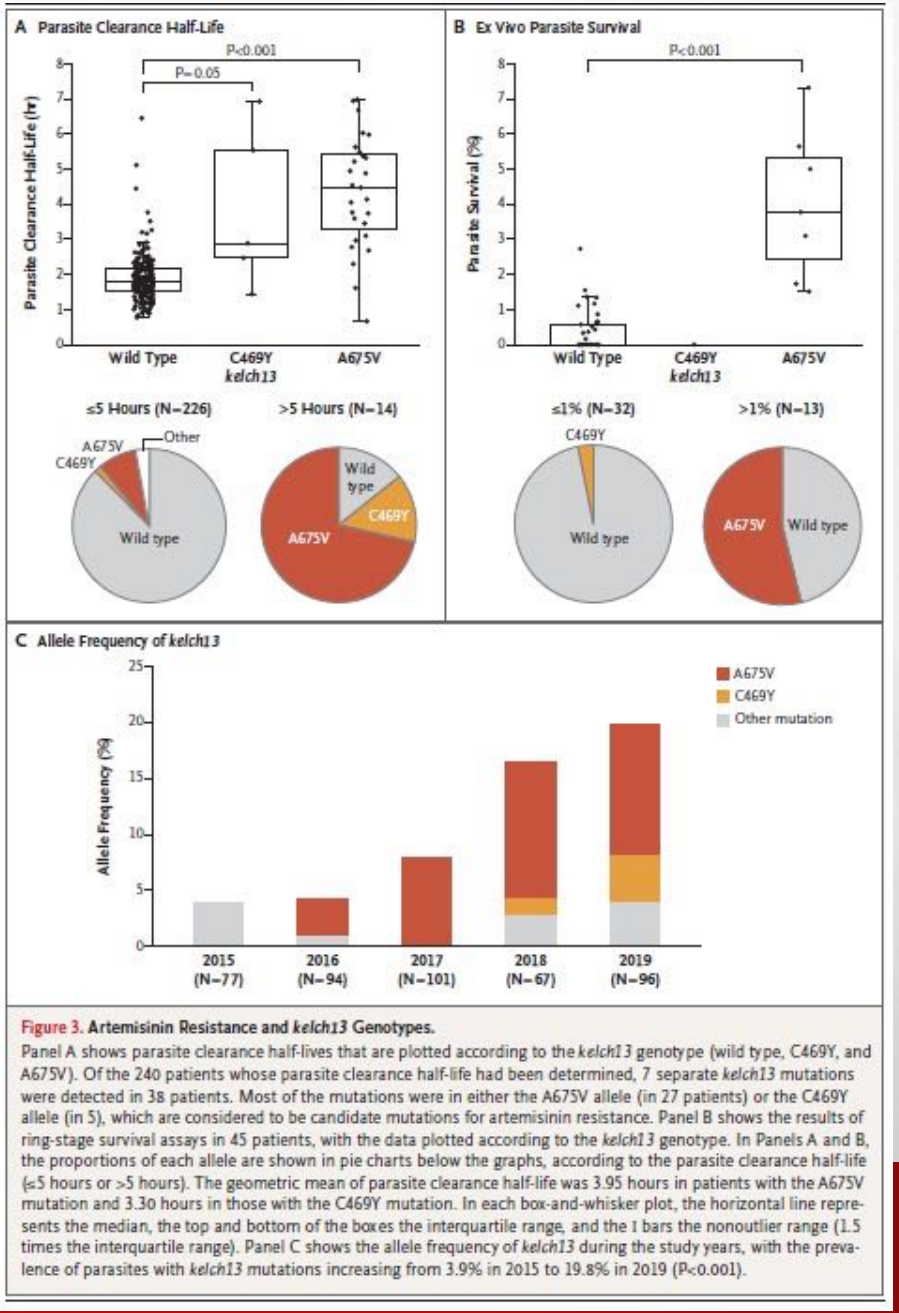

Figure 3. Artemisinin Resistance and *kelch13* Genotypes.

Panel A shows parasite clearance half-lives that are plotted according to the *kelch13* genotype (wild type, C469Y, and A675V). Of the 240 patients whose parasite clearance half-life had been determined, 7 separate *kelch13* mutations were detected in 38 patients. Most of the mutations were in either the A675V allele (in 27 patients) or the C469Y allele (in 5), which are considered to be candidate mutations for artemisinin resistance. Panel B shows the results of ring-stage survival assays in 45 patients, with the data plotted according to the *kelch13* genotype. In Panels A and B, the proportions of each allele are shown in pie charts below the graphs, according to the parasite clearance half-life (≤5 hours or >5 hours). The geometric mean of parasite clearance half-life was 3.95 hours in patients with the A675V mutation and 3.30 hours in those with the C469Y mutation. In each box-and-whisker plot, the horizontal line represents the median, the top and bottom of the boxes the interquartile range, and the I bars the nonoutlier range (1.5 times the interquartile range). Panel C shows the allele frequency of *kelch13* during the study years, with the prevalence of parasites with *kelch13* mutations increasing from 3.9% in 2015 to 19.8% in 2019 (P<0.001).

DISCUSIÓN

- LA ASOCIACIÓN QUE HEMOS ENCONTRADO ENTRE LA RESISTENCIA CLÍNICA A LA ARTEMISININA Y LA PRESENCIA DE LAS MUTACIONES DE LAS MUTACIONES A675V Y C469Y PLANTEA POSIBILIDAD QUE ESTOS MARCADORES DE RESISTENCIA PUEDAN AYUDAR A DETECTAR LA RESISTENCIA A LA ARTEMISININA ENTRE LOS PACIENTES CON INFECCIÓN POR P. FALCIPARUM EN ÁFRICA.

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Empagliflozin in Heart Failure with a Preserved Ejection Fraction

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INTRODUCCIÓN

EMPEROR-Preserved trial

MÉTODO

- ENSAYO ALEATORIZADO, DOBLE CIEGO, DOBLE CIEGO, DE GRUPOS PARALELOS, CONTROLADO CON PLACEBO CONTROLADO POR EVENTOS.
- . EL COMITÉ ÉTICO DE CADA CENTRO DE CADA CENTRO APROBÓ EL ENSAYO, Y TODOS LOS PACIENTES TODOS LOS PACIENTES DIERON SU CONSENTIMIENTO INFORMADO POR ESCRITO.
- CRITERIOS DE INCLUSIÓN:
  - LOS PARTICIPANTES ERAN HOMBRES O MUJERES DE 18 AÑOS MAYORES DE 18 AÑOS, CON INSUFICIENCIA CARDÍACA CRÓNICA DE CLASE FUNCIONAL II-IV DE LA NEW YORK HEART ASSOCIATION.
  - CLASE FUNCIONAL II-IV DE LA NEW YORK HEART ASSOCIATION Y UNA FRACCIÓN DE EYECCIÓN DEL VENTRÍCULO IZQUIERDO SUPERIOR AL 40%.
  - UN NIVEL DE NT-PROBNP DE MÁS DE 300 PG/ML O, PARA LOS PACIENTES CON FIBRILACIÓN AURICULAR EN EL MOMENTO INICIAL, UN NIVEL DE NT-PROBNP SUPERIOR A MÁS DE 900 PG/ML.

MÉTODO

- TRAS UN PERIODO DE CRIBADO DE 4 A 28 DÍAS, LOS PACIENTES SE ASIGNÓ ALEATORIAMENTE A LOS PACIENTES ELEGIBLES EN UNA PROPORCIÓN DE 1:1 Y EN MODO DOBLE CIEGO A RECIBIR O BIEN PLACEBO O EMPAGLIFLOZINA, 10 MG AL DÍA, ADEMÁS DEL TRATAMIENTO HABITUAL.
- LA ALEATORIZACIÓN SE REALIZÓ CON UN DISEÑO DE BLOQUES PERMUTADOS Y SE ESTRATIFICÓ POR REGIÓN GEOGRÁFICA, ESTADO DE LA DIABETES TASA DE FILTRACIÓN GLOMERULAR ESTIMADA (TFGE) DE MENOS DE 60 ML POR MINUTO Y FRACCIÓN DE EYECCIÓN DEL VENTRÍCULO IZQUIERDO DE MENOS DEL 50%

MÉTODO

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patient; patients who identified with more than one race or with no race were classified as other.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Two patients with an ejection fraction of exactly 40% underwent randomization and were included in the analysis.

RESULTADOS

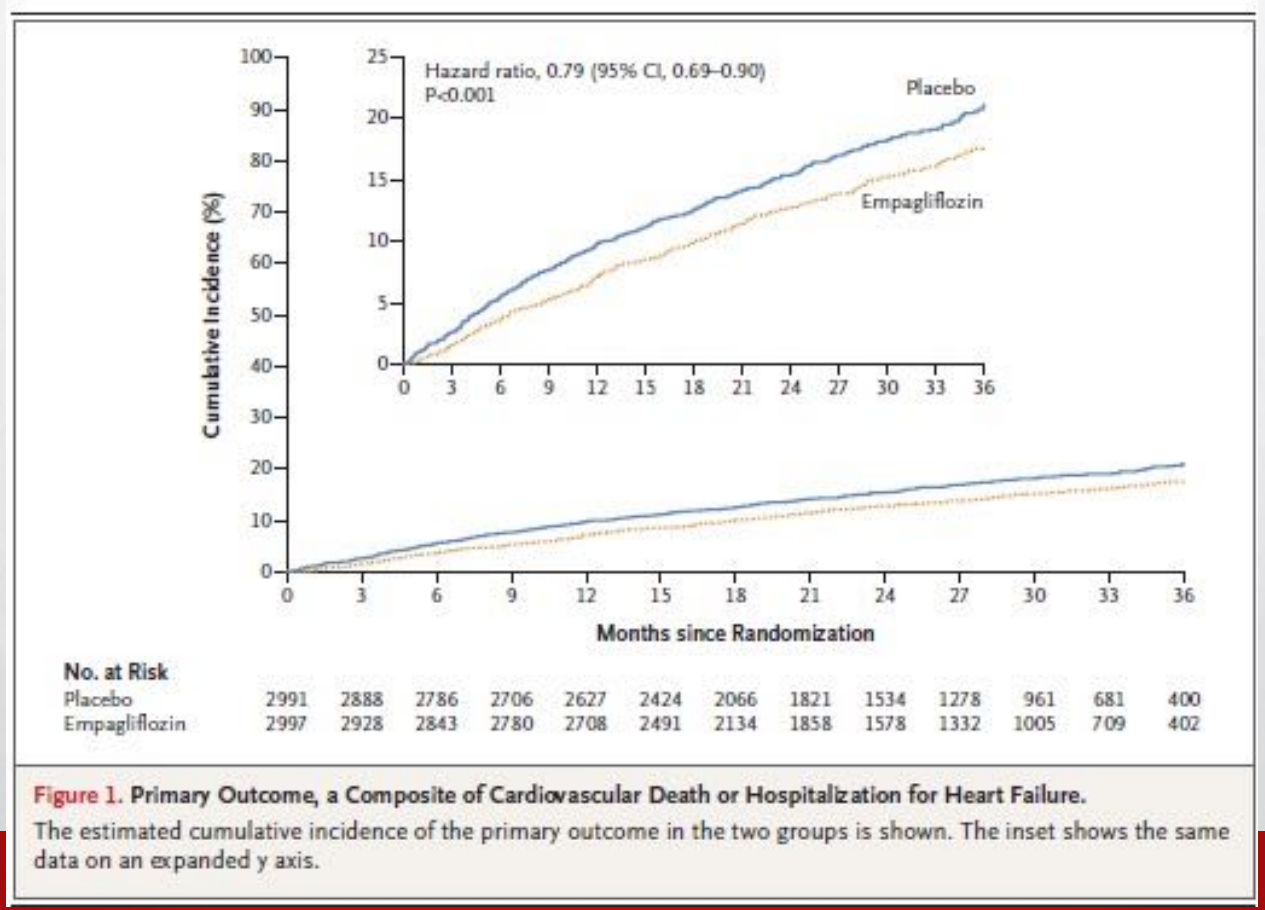


Figure 1. **Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.**
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

RESULTADOS

Table 2. Primary and Secondary Cardiovascular Outcomes.*

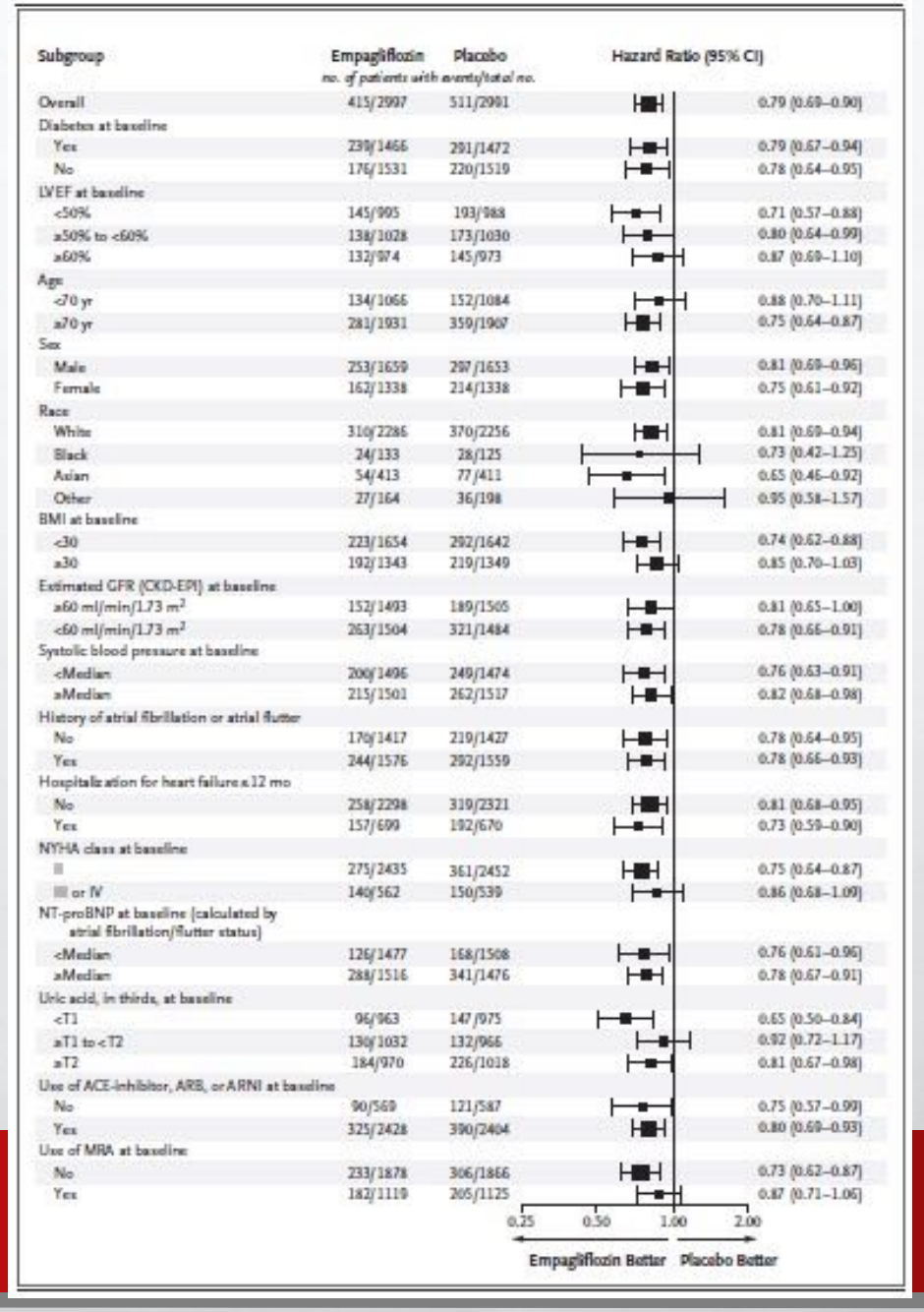
Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		*events per 100 patient-yr*		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m²†	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07)	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15)	

* All treatment effects are shown as hazard ratios, except for the slope of the change in the eGFR and the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score. For all hazard ratios or treatment differences without P values, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

† The eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) slope is analyzed on the basis of on-treatment data, using a random intercept–random slope model including age, baseline eGFR, and baseline left ventricular ejection fraction as linear covariates and sex, geographic region, baseline diabetes status, and baseline-by-time and treatment-by-time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.

‡ Change from baseline in KCCQ clinical summary score (scores range from 0 to 100, with higher scores indicating fewer or less severe symptoms or physical limitations) was analyzed with a mixed model for repeated measures, including age, baseline eGFR (CKD-EPI formula based on creatinine), and baseline left ventricular ejection fraction as linear covariates and baseline score-by-visit, visit-by-treatment, sex, geographic region, last projected visit based on dates of randomization and trial closure, and baseline diabetes status as fixed effects. The analysis is based on on-treatment data. The number of patients with available measurements for the KCCQ at week 52 in the empagliflozin and placebo groups are 2333 and 2335, respectively.

RESULTADOS



Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/905	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69–0.96)
Female	162/1338	214/1338	0.75 (0.61–0.92)
Race			
White	310/2286	370/2256	0.81 (0.69–0.94)
Black	24/133	28/125	0.73 (0.42–1.25)
Asian	54/413	77/411	0.65 (0.46–0.92)
Other	27/164	36/198	0.95 (0.58–1.57)
BMI at baseline			
<30	223/1654	292/1642	0.74 (0.62–0.88)
≥30	192/1343	219/1349	0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline			
≥60 ml/min/1.73 m^2	152/1493	189/1505	0.81 (0.65–1.00)
<60 ml/min/1.73 m^2	263/1504	321/1484	0.78 (0.66–0.91)
Systolic blood pressure at baseline			
<Median	200/1496	249/1474	0.76 (0.63–0.91)
≥Median	215/1501	262/1517	0.82 (0.68–0.98)
History of atrial fibrillation or atrial flutter			
No	170/1417	219/1427	0.78 (0.64–0.95)
Yes	244/1576	292/1559	0.78 (0.66–0.93)
Hospitalization for heart failure ≤12 mo			
No	258/2298	319/2321	0.81 (0.68–0.95)
Yes	157/699	192/670	0.73 (0.59–0.90)
NYHA class at baseline			
II	275/2435	361/2452	0.75 (0.64–0.87)
III or IV	140/562	150/539	0.86 (0.68–1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)			
<Median	126/1477	168/1508	0.76 (0.61–0.96)
≥Median	288/1516	341/1476	0.78 (0.67–0.91)
Uric acid, in thirds, at baseline			
<T1	96/963	147/975	0.65 (0.50–0.84)
≥T1 to <T2	130/1032	132/966	0.92 (0.72–1.17)
≥T2	184/970	226/1018	0.81 (0.67–0.98)
Use of ACE-inhibitor, ARB, or ARNI at baseline			
No	90/569	121/587	0.75 (0.57–0.99)
Yes	325/2428	390/2404	0.80 (0.69–0.93)
Use of MRA at baseline			
No	233/1878	306/1866	0.73 (0.62–0.87)
Yes	182/1119	205/1125	0.87 (0.71–1.06)

RESULTADOS

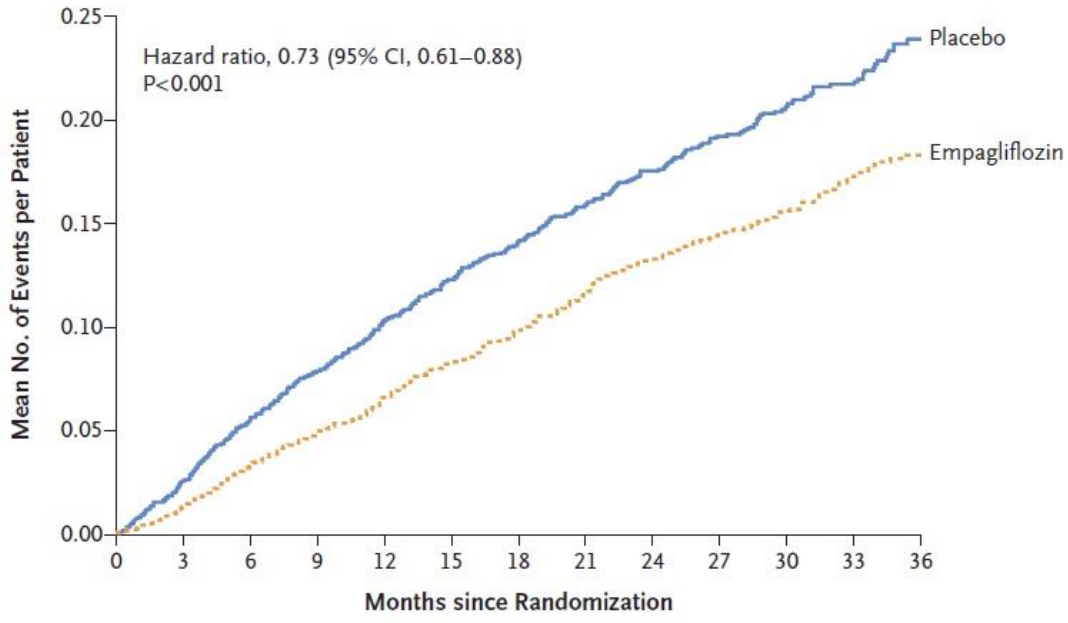


Figure 3. Hospitalizations for Heart Failure.

The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

DISCUSIÓN

- NUESTROS RESULTADOS MUESTRAN QUE EMPAGLIFLOZINA REDUJO EL RIESGO DE MUERTE CARDIOVASCULAR U HOSPITALIZACIÓN DE MUERTE CARDIOVASCULAR U HOSPITALIZACIÓN POR INSUFICIENCIA CON INSUFICIENCIA CARDÍACA Y FRACCIÓN DE EYECCIÓN CONSERVADA.
- ESTE BENEFICIO FUE CONSISTENTE EN TODOS LOS SUBGRUPOS PREESPECIFICADOS DE LA FRACCIÓN DE EYECCIÓN Y SE OBSERVÓ EN PACIENTES CON O SIN DIABETES.


GRACIAS