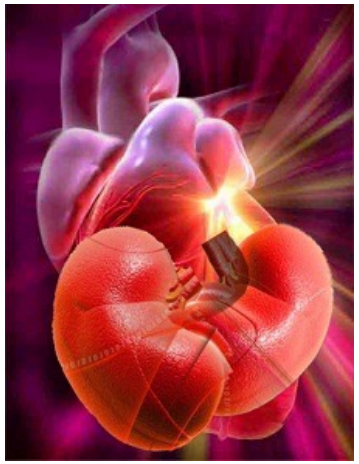
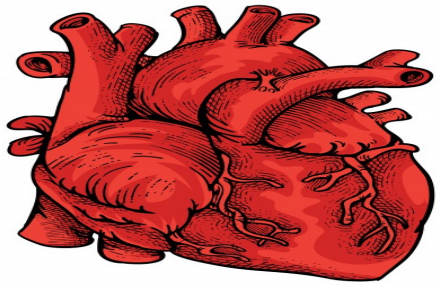


GRUPO DE INSUFICIENCIA CARDÍACA Y FIBRILACIÓN AURICULAR

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

INSUFICIENCIA CARDIACA: LO QUE DEBES SABER



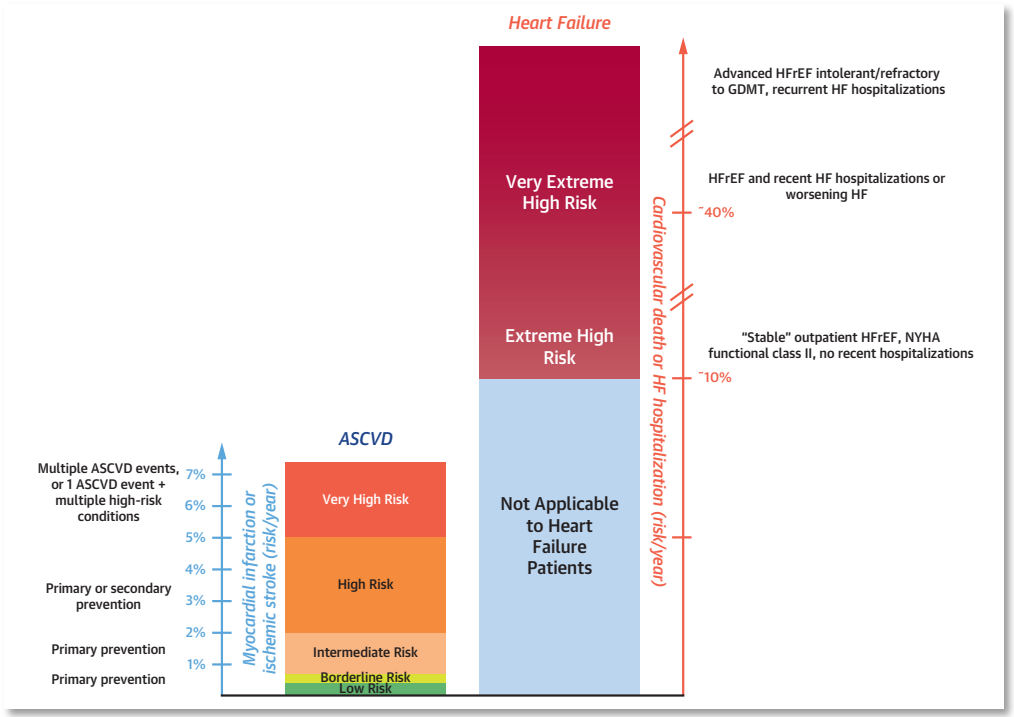
José María Fernández Rodríguez
Área Cardiorenometabólica Medicina Interna del Hospital Ramón y Cajal
Presidente de la Sociedad Asturiana de Medicina Interna

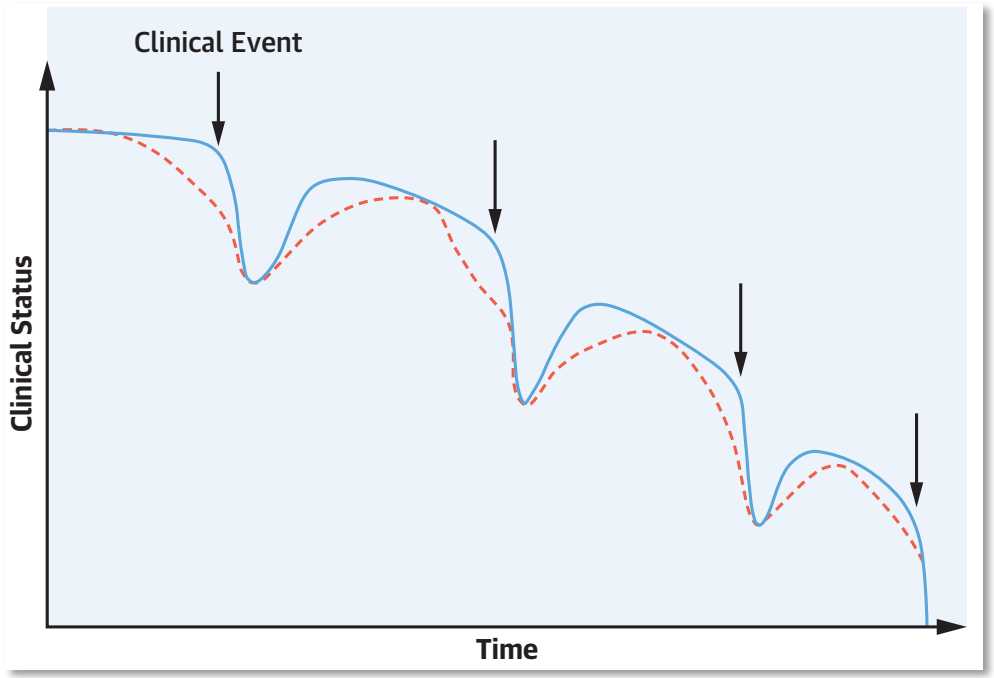
@chemachir

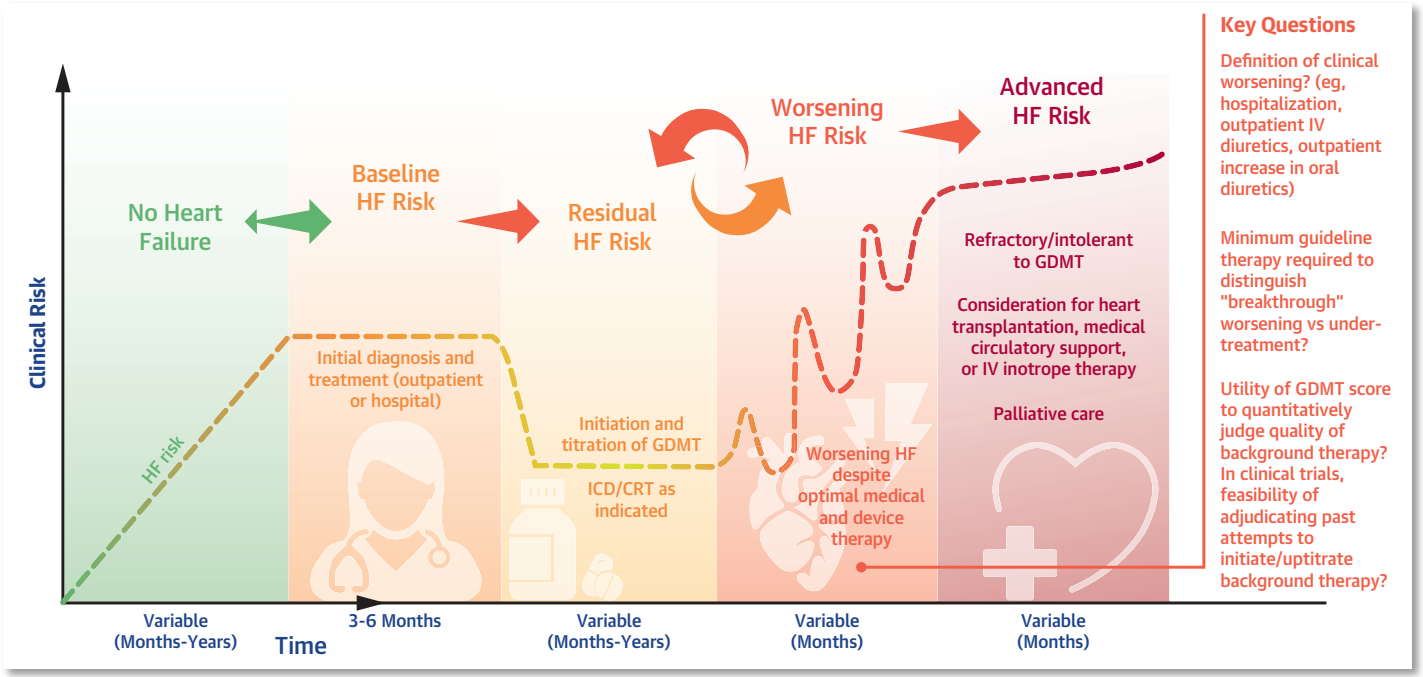
JACC REVIEW TOPIC OF THE WEEK

Worsening Heart Failure: Nomenclature, Epidemiology, and Future Directions

JACC Review Topic of the Week

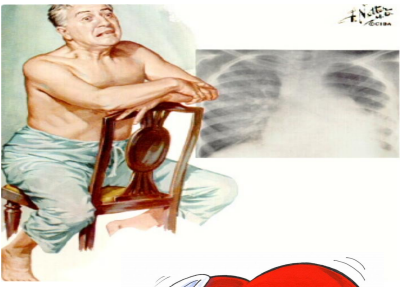


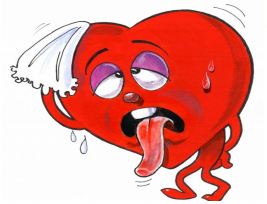




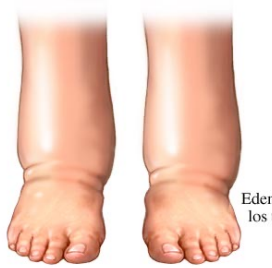
Greene SJ, et al. J Am Coll Cardiol. 2023;81(4):413–424.

Los pacientes hospitalizados por IC incrementan 2.5 veces el riesgo de mortalidad





POR ELLO EL MOMENTO DE LA AGUDIZACIÓN ES EL DE MÁXIMA VULNERABILIDAD Y EL DE LLEVAR A CABO UN PUNTO DE INFLEXIÓN



Edema (hinchazón) de los tobillos y los pies

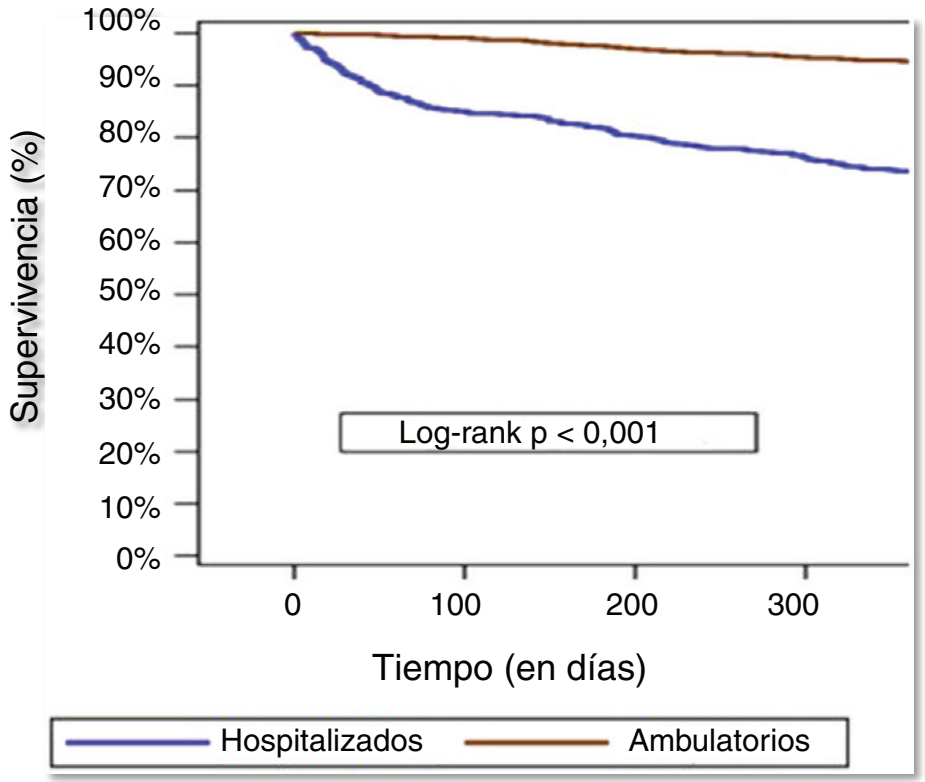
CI, confidence interval; HF, heart failure; HFH, HF hospitalization; HR, hazard ratio

Ahmed et al. J Card Fail 2008;14:211-18

Artículo original

Pronóstico al año en pacientes con insuficiencia cardiaca en España. Registro ESC-EORP-HFA Heart Failure Long-Term

María G. Crespo-Leiro[a,b,], Eduardo Barge-Caballero[a,b], Javier Segovia-Cubero[b,c], José González-Costello[d], Antoni Bayés-Genís[b,e], Silvia López-Fernández[f], Sonia Mirabet-Pérez[g], Marisa Sanz-Julve[h], Carla Fernández-Vivancos[i], José María Pérez-Ruiz[j], José Manuel García-Pinilla[b,k], Alfonso Varela-Román[b,l], Luis Almenar-Bonet[b,m], Antonio Lara-Padrón[n], Luis de la Fuente-Galán[o], Francisco Torres-Calvo[p], Juan Carlos Arias-Castaño[q], Francisco Ridocci-Soriano[r], Javier Andrés-Novales[s], Domingo A. Pascual-Figal[b,t], David Bierge-Valero[u], Francisco Epelde[v], Juan Carlos Gallego-Page[w], Ana M. Sahuquillo-Martínez[x], Beatriz Díaz-Molina[y], Regina Dalmau González-Gallarza[z], Juan Quiles-Granado[aa], Aldo Pietro Maggioni[ab,ac], Lars H. Lund[ad], Cécile Laroche[ac] y Juan Delgado-Jiménez[b,ae]*



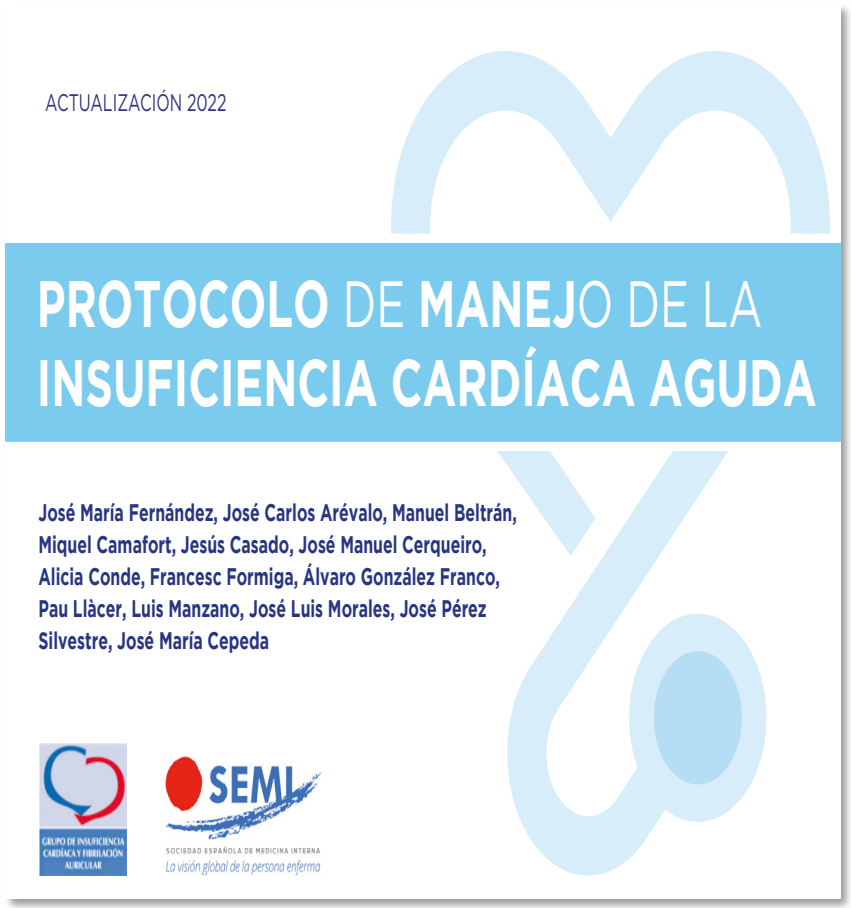
Resultados: La mortalidad al año en IC aguda fue del 29,3% en España (IC95%, 25,6-33,2) y 27,7% en el resto de Europa (p=0,4303). En IC crónica, las cifras correspondientes fueron 6,4% (IC95%, 5,4-7,5) y 9,5% (p<0,0001). La hospitalización al año por cualquier causa tras un ingreso por IC aguda en España fue de 46,2% (IC95%, 41,8-50,7) y 44,6% en Europa (p=0,4977); en IC crónica, estas cifras fueron 22,3% (IC95%, 20,6-24,1) y 30,0%, respectivamente (p<0,0001).

¿Qué novedades aporta?

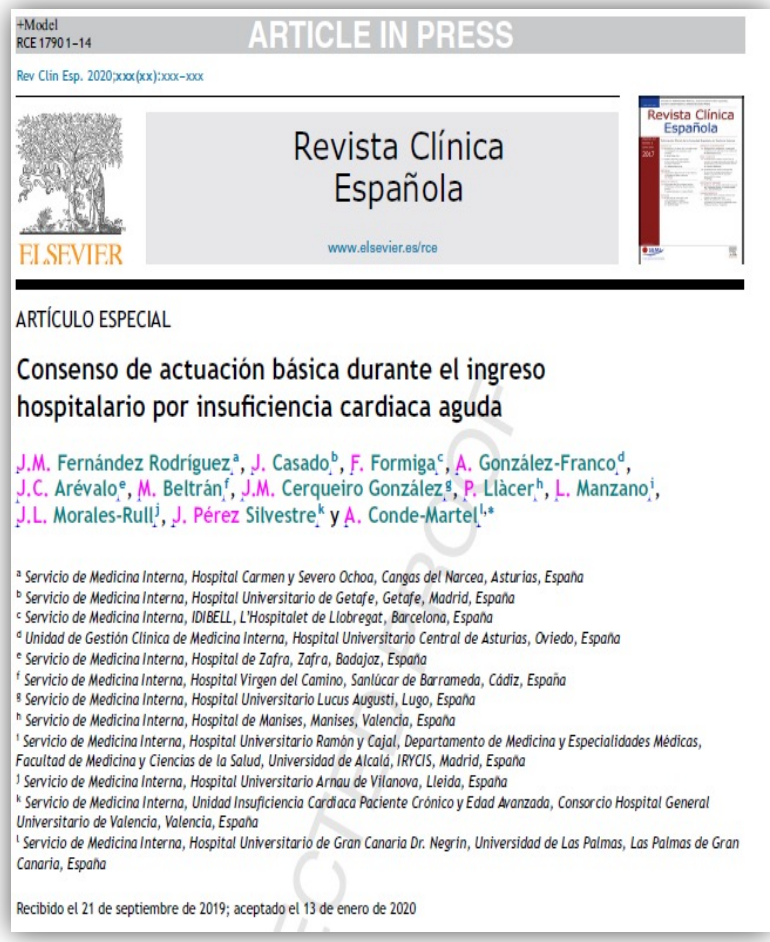
- Incluso en centros con buen cumplimiento de las guías, la IC continúa siendo una condición grave, en especial cuando ya necesita ingreso.
- Globalmente, tras un ingreso por IC en España, es de esperar que un año después casi uno de cada 3 pacientes (29,3%) haya fallecido (incluyendo el 5,9% que fallece durante el ingreso) y casi uno de cada 2 (46,4%) o bien haya fallecido o haya necesitado reingresar por IC. En los pacientes con IC crónica estas cifras son muy inferiores (6,4 y 14,0%, respectivamente), lo que confirma el alto riesgo asociado a la necesidad de ingreso.

Crespo-LeiroMG,etal.Pronósticoalañ oenpacientesconinsuficienciacardiacaenEspañ a.RegistroESC-EORP-HFA Heart Failure Long-Term. *REC CardioClinics.* 2020. https://doi.org/10.1016/j.rccl.2020.02.001

ACTUALIZACIÓN PROTOCOLO ICA 2022



1. CONSIDERACIONES AL INGRESO.
2. MANEJO FASE CONGESTIVA.
3. MANEJO EN FASE ESTABLE.
4. CONSIDERACIONES AL ALTA.



@IcyfaSemi

Fernández Rodríguez JM, et al. Consenso de actuación básica durante el ingreso hospitalario por insuficiencia cardiaca aguda. Rev Clin Esp. 2020. https://doi.org/10.1016/j.rce.2020.01.002

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

FÁRMACOS MODIFICADORES DE LA ENFERMEDAD (BB, ARNI, ARM)*:

Sólo retirar si:

- Inestabilidad hemodinámica
- Hiperpotasemia (K^+>6)
- Creat >2,5 / descenso del FGe del 50% respecto al basal

- pH 7,25-7,34
- 25 rpm
- Consciente

→ ☐ VMNI → BIPAP (Si acidosis respiratoria) / CPAP (Si $PaCO_2$<50)

- pH < 7,25 o
- Bajo nivel de consciencia o
- Saturación O_2<90% (o PaO_2<60) a pesar de VMNI

→ ☐ IOT

SOPORTE HEMODINÁMICO:

Nitroglicerina iv (en casos de ICA con hipertensión [PAs >160 mmHg] y/o EAP)

- Monitorización horaria de PA
- Si PAs <90 mmHg: retirar

PA<90 mmHg:

1. Retirada o reducción de dosis de antihipertensivos concomitantes.
2. Si asocia síntomas de hipoperfusión iniciar inotrópicos
   - LEVOSIMENDÁN (sobretodo si BB)
   - DOBUTAMINA

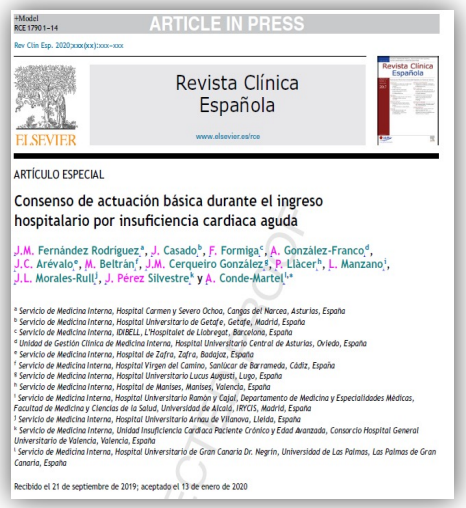
VASOCONSTRICTORES (si shock cardiogénico [PA <90 mmHg])

Hasta conseguir PA >90 mmHg, combinar con inotrópicos hasta la retirada de vasoconstrictores

Precisa monitorizar PA y ECG

- **NORADRENALINA (preferente)**
- DOPAMINA

Si fracaso, valorar dispositivos implantables


ARTICLE IN PRESS

Revista Clínica Española

ARTÍCULO ESPECIAL

Consenso de actuación básica durante el ingreso hospitalario por insuficiencia cardiaca aguda

J.M. Fernández Rodríguez[a], J. Casado[b], F. Formiga[c], A. González-Franco[d], J.C. Arévalo*, M. Beltrán[f], J.M. Cerqueiro González[g], P. Llácer[h], L. Manzano[i], J.L. Morales-Ruil[j], J. Pérez Silvestre[k] y A. Conde-Martel[l,*]

Recibido el 21 de septiembre de 2019; aceptado el 13 de enero de 2020

- Los antagonistas neurohormonales han mejorado dramáticamente los resultados para HFrEF. ***Cuando sea posible, hay que mantener la terapia modificadora de la enfermedad (GDMT) durante la hospitalización o iniciaciarla antes del alta*** ya que se asocia con resultados sustancialmente mejores.

Fernández Rodríguez JM, et al. Consenso de actuación básica durante el ingreso hospitalario por insuficiencia cardiaca aguda. Rev Clin Esp. 2020. https://doi.org/10.1016/j.rce.2020.01.002

Heidenreich *et al*
2022 AHA/ACC/HFSA Heart Failure Guideline https://doi.org/10.1016/j.jacc.2021.12.012

Heart Failure Hospitalization and Guideline-Directed Prescribing Patterns Among Heart Failure With Reduced Ejection Fraction Patients

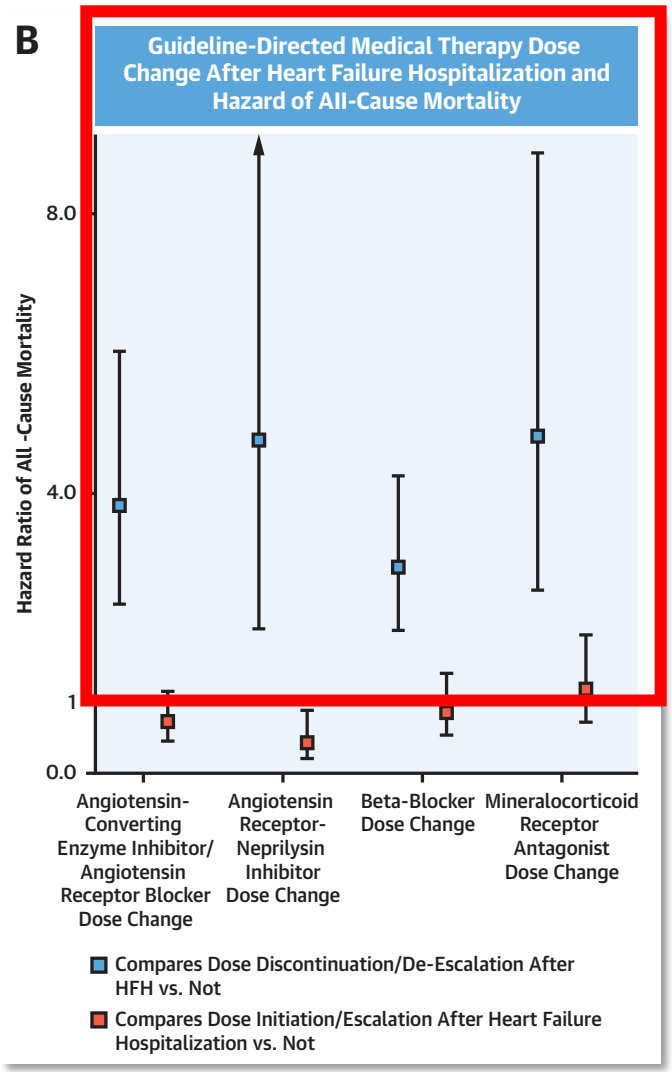
Pratyaksh K. Srivastava, MD,[a] Adam D. DeVore, MD, MHS,[b,c] Anne S. Hellkamp, MS,[b] Laine Thomas, PhD,[b] Nancy M. Albert, PhD,[d] Javed Butler, MD, MPH, MBA,[e] J. Herbert Patterson, PharmD,[f] John A. Spertus, MD, MPH,[g] Fredonia B. Williams, EdD,[h] Carol I. Duffy, DO,[i] Adrian F. Hernandez, MD, MHS,[b,c] Gregg C. Fonarow, MD[j]

TABLE 5 Association Between GDMT Dose Change and All-Cause Mortality Among Those With History of HFH

	N	No Dose De-Escalation/Discontinuation After HFH Events/100 pt-yrs (Total Events)	Dose De-Escalation/Discontinuation After HFH Events/100 pt-yrs (Total Events)	Dose De-Escalation/Discontinuation After HFH vs. Not Adjusted PR (95% CI)	p Value
ACE inhibitor/ARB	449	11.4 (51)	45.0 (41)	3.82 (2.42-6.03)	<0.001
ARNI	121	10.0 (11)	46.8 (16)	4.76 (2.06-11.03)	<0.001
Beta-blocker	662	13.4 (84)	36.8 (58)	2.94 (2.04-4.25)	<0.001
MRA	303	12.7 (38)	54.5 (31)	4.81 (2.61-8.87)	<0.001

	N	No Dose Initiation/Escalation After HFH Events/100 pt-yrs (Total Events)	Dose Initiation/Escalation After HFH Events/100 pt-yrs (Total Events)	Dose Initiation/Escalation After HFH vs. Not Adjusted PR (95% CI)	p Value
ACE inhibitor/ARB	603	21.6 (124)	15.7 (22)	0.73 (0.46-1.16)	0.189
ARNI	677	21.3 (150)	9.4 (9)	0.44 (0.21-0.90)	0.024
Beta-blocker	489	21.9 (105)	21.3 (19)	0.87 (0.54-1.42)	0.584
MRA	484	18.2 (85)	24.4 (24)	1.20 (0.73-1.97)	0.462

Abbreviations as in Tables 1 and 2.



- **N=4365 CON TMO previo a ingreso.**
- **La reducción de dosis o retirada innecesaria de ARNI, BB, IECAs/ARA II o ARM:**
  - ***Aumenta de tres a cinco veces la mortalidad total o los ingresos por IC.***

Srivastava, P.K. et al. J Am Coll Cardiol HF. 2021;9(1):28-38.

¿Cuándo ? ¿Cómo? ¿Y Por qué iniciar u optimizar la TME?

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

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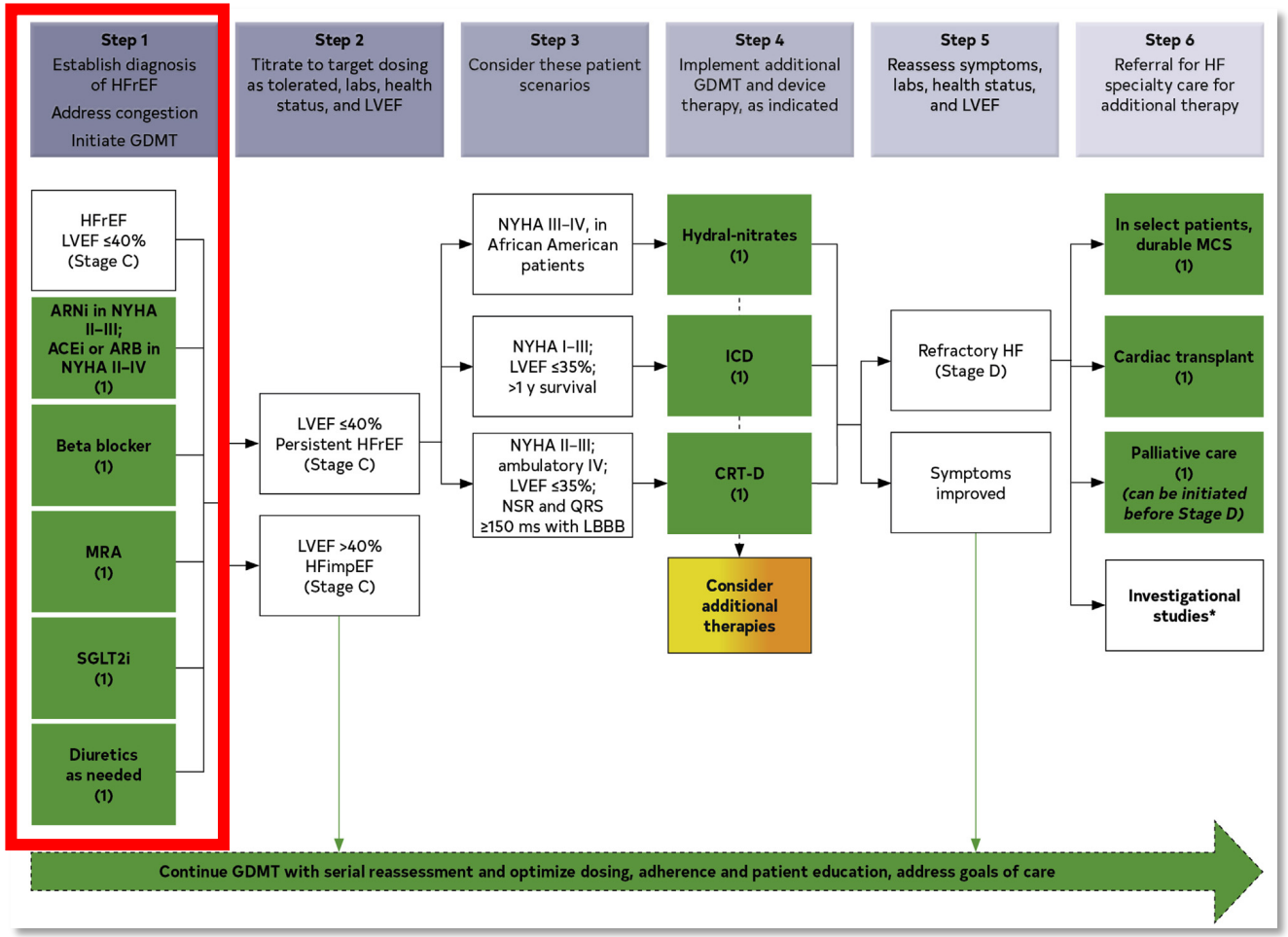
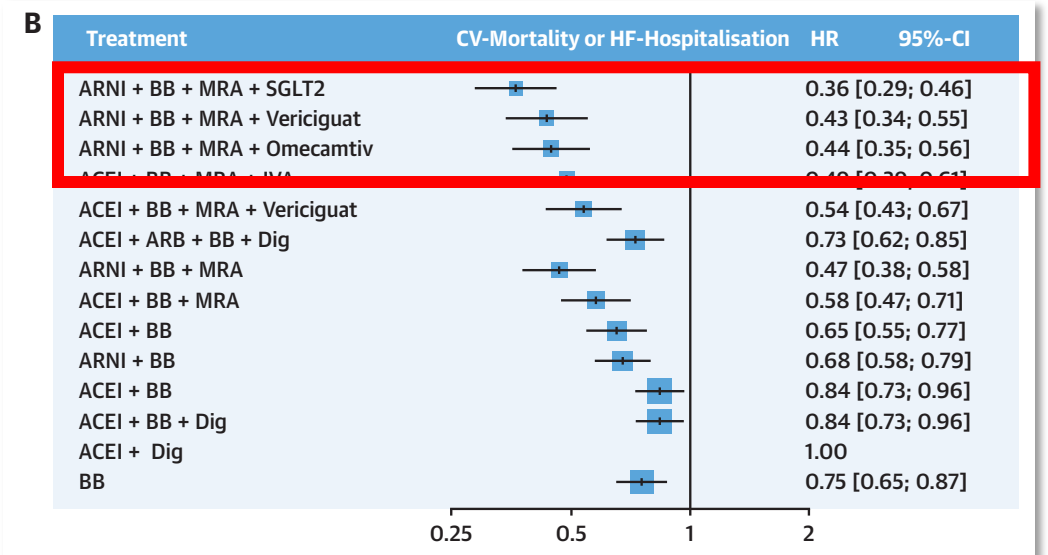
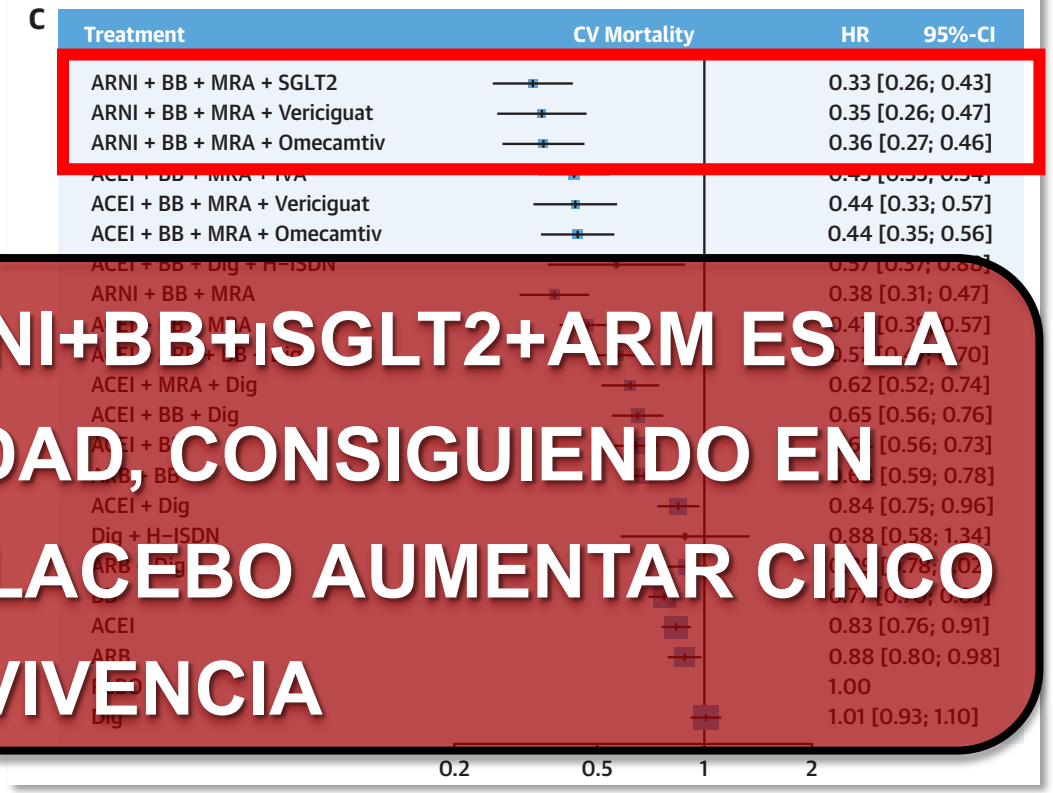
COR	LOE	RECOMMENDATIONS
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality (1-5).
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible (6-13).
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality (14-18).
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value (19-25).



Heidenreich *et al*
2022 AHA/ACC/HFSA Heart Failure Guideline
https://doi.org/10.1016/j.jacc.2021.12.012

A Systematic Review and Network-Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction





LA CUADRUPLE TERAPIA COM ARNI+BB+iSGLT2+ARM ES LA QUE MÁS REDUCE LA MORTALIDAD, CONSIGUIENDO EN MAYORES DE 70 AÑOS FRENTE A PLACEBO AUMENTAR CINCO AÑOS LA SUPERVIVENCIA

Tromp, J. et al. J Am Coll Cardiol HF. 2021;■(■):■-■.

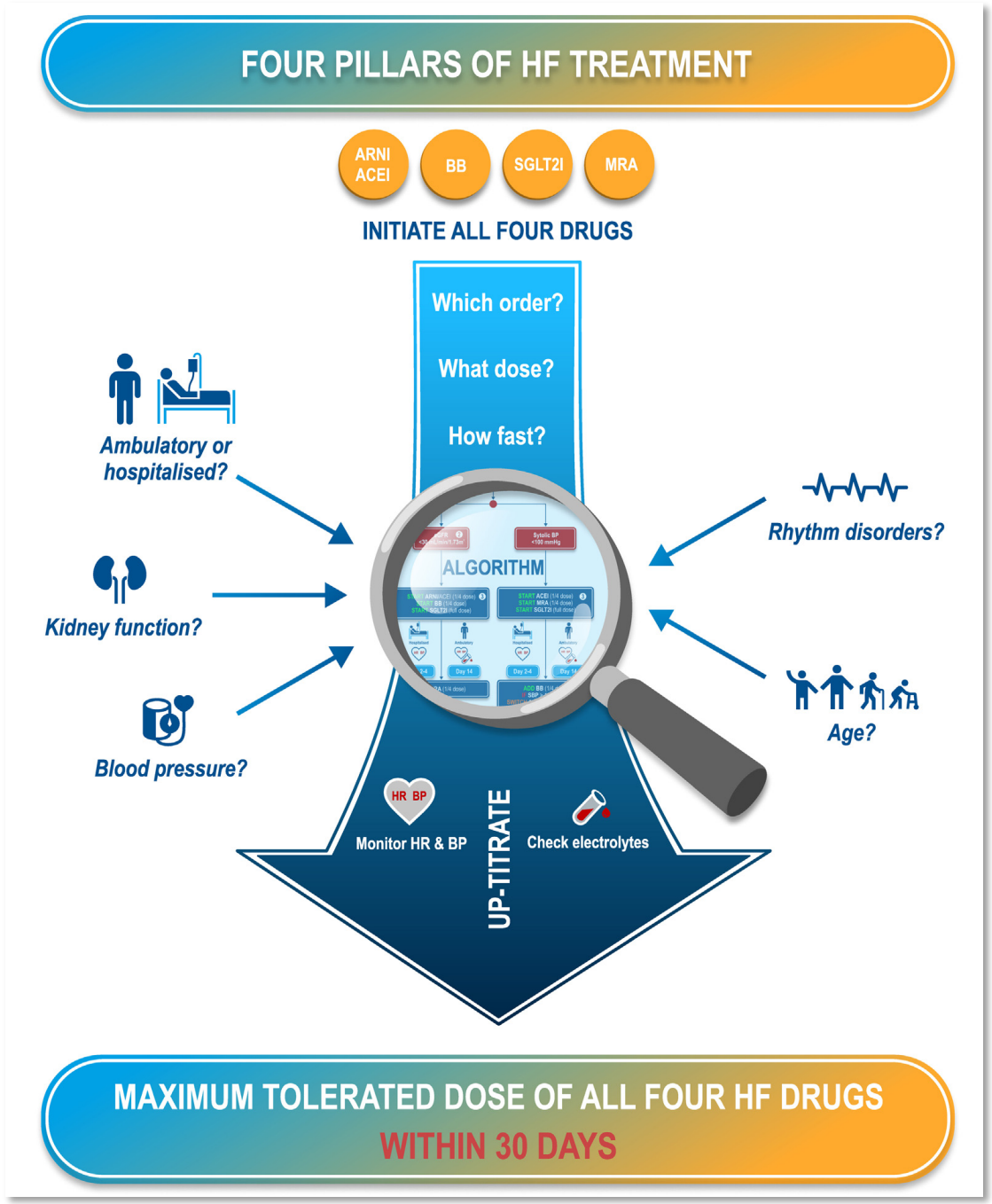
Recomendaciones	Clase[a]	Nivel[b]
Se recomienda evaluar exhaustivamente a los pacientes hospitalizados por IC para descartar signos de congestión antes del alta y optimizar el tratamiento oral[427,472]	I	C
Se recomienda la administración de tratamiento farmacológico oral basado en la evidencia antes del alta[103,513]	I	C
Se recomienda una consulta de seguimiento 1-2 semanas después del alta para descartar signos de congestión, examinar la tolerancia al tratamiento farmacológico e iniciar o ajustar el tratamiento basado en la evidencia[517,518]	I	C
Se debe considerar la carobximaltosa férrica en caso de déficit de hierro, definido como ferritina sérica < 100 ng/ml o 100-299 ng/ml con Sat-T $< 20\%$, para mejorar los síntomas y reducir las hospitalizaciones[512]	IIa	B

McDonagh TA, et al. Guía ESC 2021 sobre el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica. Rev Esp Cardiol. 2022.
https://doi.org/10.1016/j.recesp.2021.11.027

Special article

Optimisation of treatments for heart failure with reduced ejection fraction in routine practice: a position statement from a panel of experts

Nicolas Girerd,[a,b,*] Christophe Leclercq,[c,d] Olivier Hanon,[e] Antoni Bayés-Genís,[f,g] James L. Januzzi,[h,i] Thibaut Damy,[j] Benoit Lequeux,[k] Christophe Meune,[l] Pierre Sabouret,[m] and François Roubille[n]



Girerd N, et al. Optimisation of treatments for heart failure with reduced ejection fraction in routine practice: a position statement from a panel of experts. Rev Esp Cardiol. 2023. https://doi.org/10.1016/j.rec.2023.03.005

Canadian Journal of Cardiology 37 (2021) 632–643

Review

A Novel Approach to Medical Management of Heart Failure With Reduced Ejection Fraction

Robert J.H. Miller, MD,* Jonathan G. Howlett, MD,* and Nowell M. Fine, MD, SM*

Division of Cardiology, Department of Cardiac Sciences, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

"Más vale un poco de todos que mucho de uno"

Table 3. Probable relative benefits of foundational HFrEF therapy: initiation vs target dose*

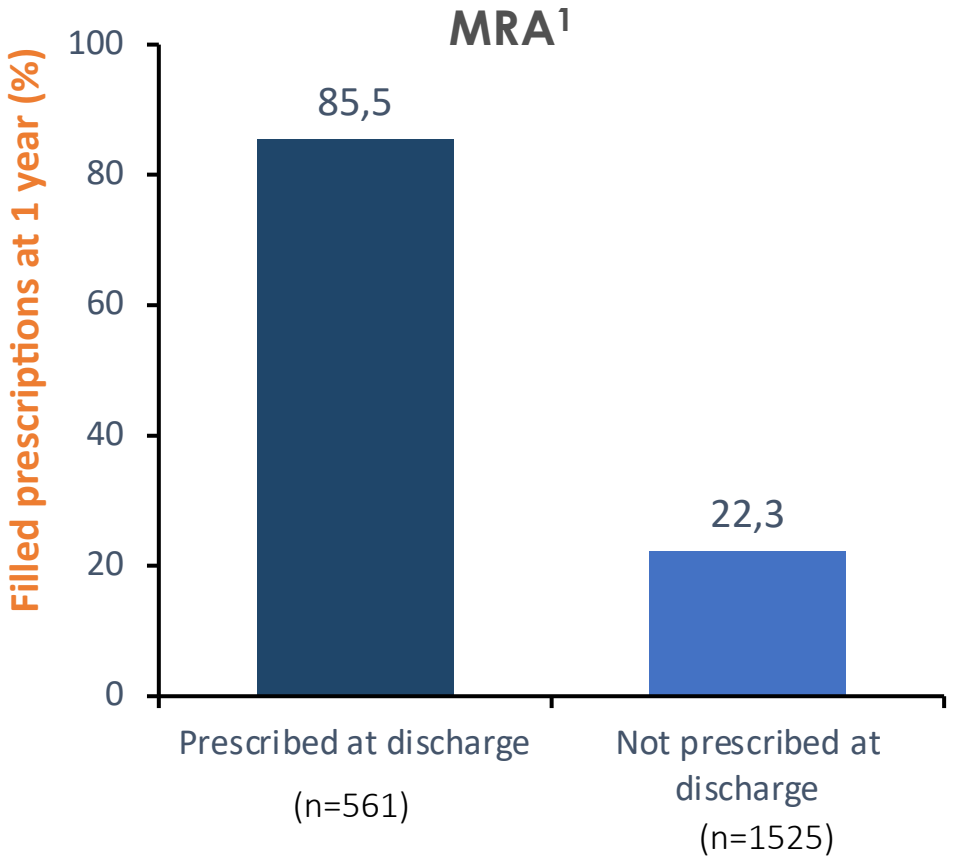
Outcome affected	Initiation of therapeutic class	Titration from initial to target dose†
Heart failure hospitalization endpoint	Up to two-thirds of overall benefit with ACE/ARB. Significant benefit with ARNI, MRA, SGLT2I observed within 4 to 6 weeks following randomization	Further ~one-third benefit in ACE Uncertain for other Foundational Therapies
Cardiovascular mortality endpoint	Improvement observed, event curves separate within 3 months following randomization	No clear further benefit with ACE, ARB Further benefit possible with MRA, β-blockers
Time course of benefits on combined cardiovascular death + heart failure hospitalization endpoint	Initial 2 to 4 weeks for all Foundational Therapies	Event curves begin to separate 6 months following randomization
Side effects	Withdrawal in < 10%	Dose-related increase in side effects
Combination with other Foundational Therapies	Additive benefits in combination	Additive benefits in combination

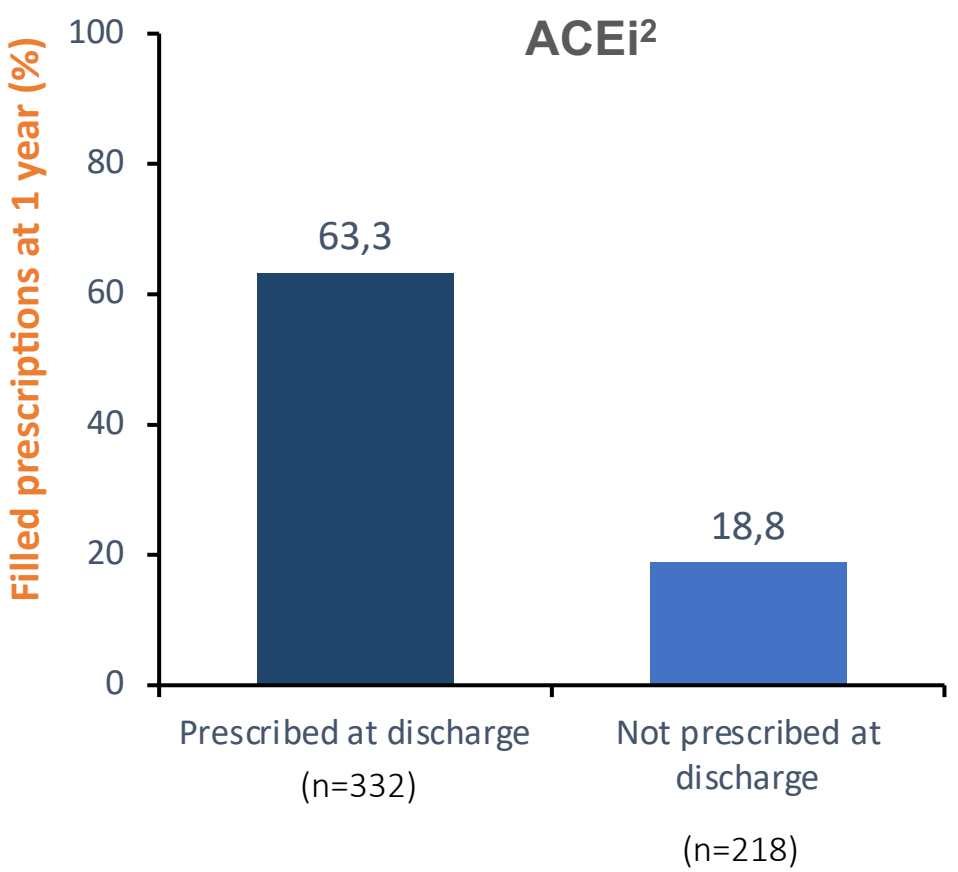
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose cotransport-2 inhibitor.

* For clarity, titration to target doses is associated with accrual of clinical benefits following drug initiation.

† SGLT2I trials have evaluated only 1 dose.

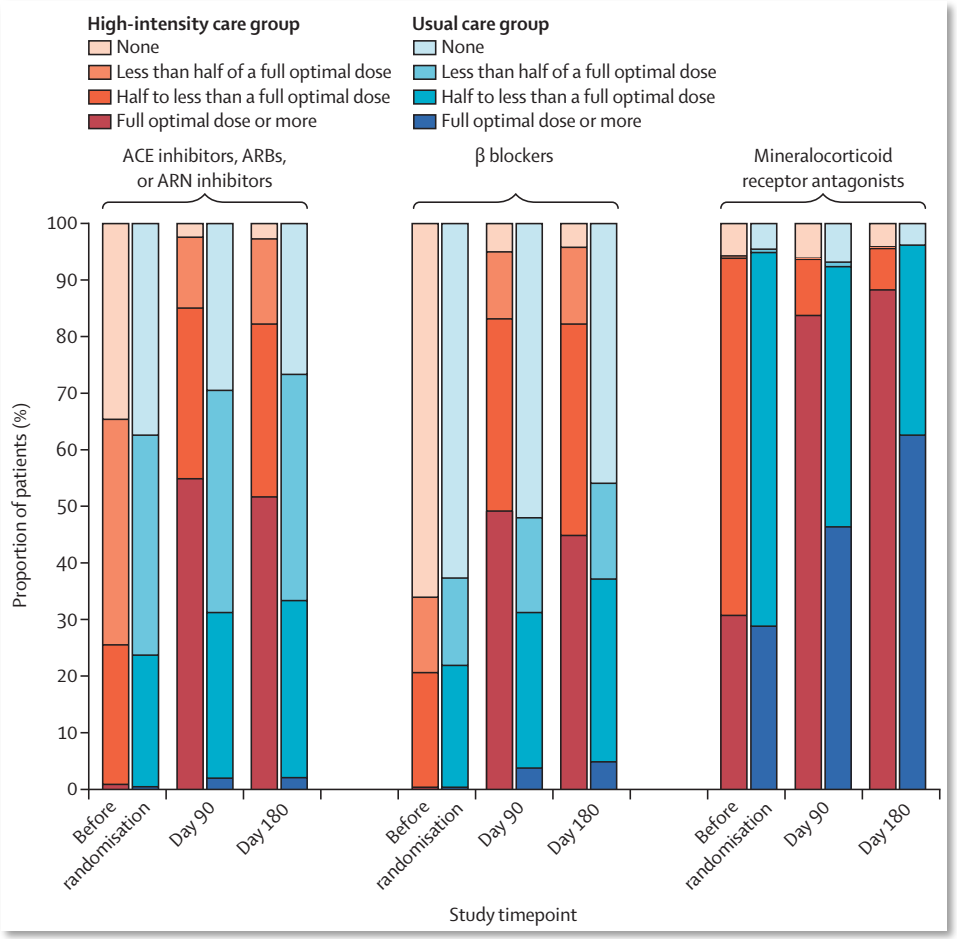
Early treatment initiation in the hospital is associated with improved adherence





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

STRONG-HF, ***El último grupo recibió una terapia de 4 fármacos rápidamente aumentada para lograr dosis óptimas dentro de las 2 semanas posteriores al alta. Este enfoque fue factible y seguro, y el ensayo demostró que la titulación rápida de GDMT redujo significativamente el riesgo de muerte por todas las causas de 180 días o de hospitalización por insuficiencia cardíaca.***



	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	Adjusted risk ratio (95% CI)	p value
Primary endpoint					
All-cause death or heart failure readmission by day 180*	74/506 (15·2%)	109/502 (23·3%)	8·1 (2·9 to 13·2)	0·66 (0·50 to 0·86)	0·0021
Secondary endpoints					
Change from baseline to day 90 in EQ-5D VAS†	10·72 (0·88)	7·22 (0·90)	3·49 (1·74 to 5·24)	NA	<0·0001
All-cause death by day 180*	39/506 (8·5%)	48/502 (10·0%)	1·6 (−2·3 to 5·4)	0·84 (0·56 to 1·26)	0·42
All-cause death or heart failure readmission by day 90*	55 (10·4%)	72 (13·8%)	3·4 (−0·4 to 7·3)	0·73 (0·53 to 1·02)	0·081
Prespecified exploratory endpoints					
Cardiovascular death by day 180*	32/506 (6·9%)	44/502 (9·3%)	2·4 (−1·2 to 6·1)	0·74 (0·47 to 1·16)	0·19
Cardiovascular death by day 90*	17 (3·3%)	28 (5·4%)	2·1 (−0·3 to 4·6)	0·60 (0·33 to 1·09)	0·086
All-cause death by day 90*	23 (4·3%)	30 (5·7%)	1·4 (−1·2 to 4·0)	0·76 (0·45 to 1·29)	0·28
Heart failure readmission by day 180*	47/506 (9·5%)	74/502 (17·1%)	7·6 (3·0 to 12·1)	0·56 (0·38 to 0·81)	0·0011
Heart failure readmission by day 90*	36 (6·9%)	48 (9·5%)	2·5 (−0·8 to 5·8)	0·67 (0·43 to 1·04)	0·13
Finkelstein-Schoenfeld hierarchical composite‡	..	..	1·28 (1·13 to 1·46)	NA	0·0002
Proportion of comparisons where group is superior§	40·4%	29·4%	..	..	..
Proportion of comparisons where groups are tied	30·2%	NA	..	..	..
Sensitivity analyses					
All-cause death or heart failure readmission by day 180, excluding COVID-19 deaths*	69/506 (14·1%)	108/502 (23·0%)	8·9 (3·9 to 14·0)	0·61 (0·46 to 0·82)	0·0005
All-cause death by day 180, excluding COVID-19 deaths*	33/506 (7·1%)	47/502 (9·8%)	2·7 (−1·0 to 6·4)	0·72 (0·47 to 1·12)	0·15

www.thelancet.com **Published online November 7, 2022 https://doi.org/10.1016/S0140-6736(22)02076-1**

ACTUALIZACIÓN PROTOCOLO ICA 2022

GRUPO DE INSUFICIENCIA CARDÍACA Y FIBRILACIÓN AURICULAR

MANEJO FASE ESTABLE

DIURÉTICOS: Reducir hasta su paso a vía oral y a la dosis mínima eficaz

INICIO O AJUSTE DE FÁRMACOS MODIFICADORES DE LA ENFERMEDAD (IC-FEr de novo o previa)

En pacientes con IC-FEr:

- Máximo aumento de la supervivencia: ARNI y BB, con lo que son prioritarios
- Situación ideal sería iniciar la cuádruple terapia durante el ingreso: ARNI+BB+iSGLT2+ARM
- En fase congestiva: ARNI y empagliflozina
- Euvolémico: BB (con menos evidencia en fase aguda ARM)

En pacientes con FEVI ≥40% empagliflozina reduce la mortalidad y los ingresos por IC

En pacientes con FEVI entre 41-49% podría considerarse usar BB, ARNI, IECA, ARAII y ARM

☐ **ARNI**

☐ Se considerará el uso de IECA/ARAII en aquellos casos que no puedan tomar ARNI, por la causa que fuera

☐ **BETABLOQUEANTE** (Si la FA y FC lo permiten mantener al ingreso o inicial)

- **Si RS → objetivo FC: 50-70 lpm** (no subir dosis de BB si FC <60 lpm)
- **Si FA → objetivo FC: 60-100 lpm** (óptima 70-90 lpm), máx 110 lpm (no existe un claro beneficio de BB)
- **Si RS y FC ≥70 lpm con BB** a dosis máxima tolerada → valorar ivabradina

☐ **ARM:** utilizar la dosis neurohormonal (25-50 mg/24h)

@IcyfaSemi

Posible nueva actualización desde la publicada en :Fernández Rodríguez JM, et al. Consenso de actuación básica durante el ingreso hospitalario por insuficiencia cardiaca aguda. Rev Clin Esp. 2020. https://doi.org/10.1016/j.rce.2020.01.002

ELSEVIER

Canadian Journal of Cardiology 37 (2021) 632–643

Review

A Novel Approach to Medical Management of Heart Failure With Reduced Ejection Fraction

Robert J.H. Miller, MD,* Jonathan G. Howlett, MD,* and Nowell M. Fine, MD, SM*

Division of Cardiology, Department of Cardiac Sciences, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Los "Fármacos Fundamentales" se agrupan en tres grupos generales con similares efectos hemodinámicos y/o neurohormonales. Los fármacos **dentro de cada grupo no deben iniciarse u optimizarse en la misma visita** debido a **posibles efectos secundarios,** pero se deben hacer intentos para **optimizar cada grupo durante cada consulta** (hasta 3 cambios por consulta).

Cluster Scheme

Initiation and Titration of Foundational Therapy for Heart Failure with LVEF < 40%

Red- Face to face visit with prescriber preferred | Blue- Either face to face or virtual visit with prescriber | Orange- Virtual visit with prescriber preferred

Recommended Total Time for Titration ≤ 12 weeks (3 months)

Cluster A: Diuretic & SGLTi +	Cluster B: ARNi & MRA +	Cluster C: Beta Blocker & SNI*
Encounter 1 (Usually face-to-face, up to 3 medication initiations)		
Start Preferred Cluster A Medication	Start Preferred Cluster B Medication	Start Preferred Cluster Medication*
1- 2 Weeks		
Encounter 2 (whenever feasible, up to 3 medication initiations)		
Titrate Cluster A Medication	Start Second Cluster B Medication	Adjust Cluster C Medication*
1- 2 Weeks		
Encounter 3 & ongoing (whenever feasible, up to 3 medication titrations)		
Diuretic titration as needed	Cluster B Medication titration	Cluster C Medication Titration*
1- 2 Weeks		
Goal Foundational Therapy- Continue to actively manage as necessary Addition of Personalized Therapies as dictated by clinical presentation and setting (see Table 2)		

Los pacientes no frágiles con **TAS > 110 mm Hg, FC en reposo> 70 latidos por minuto, TFGe> 40 ml/min y K+ sérico <5,0 mmol / L generalmente pueden tolerar tres cambios de medicación** con una baja tasa de efectos secundarios.

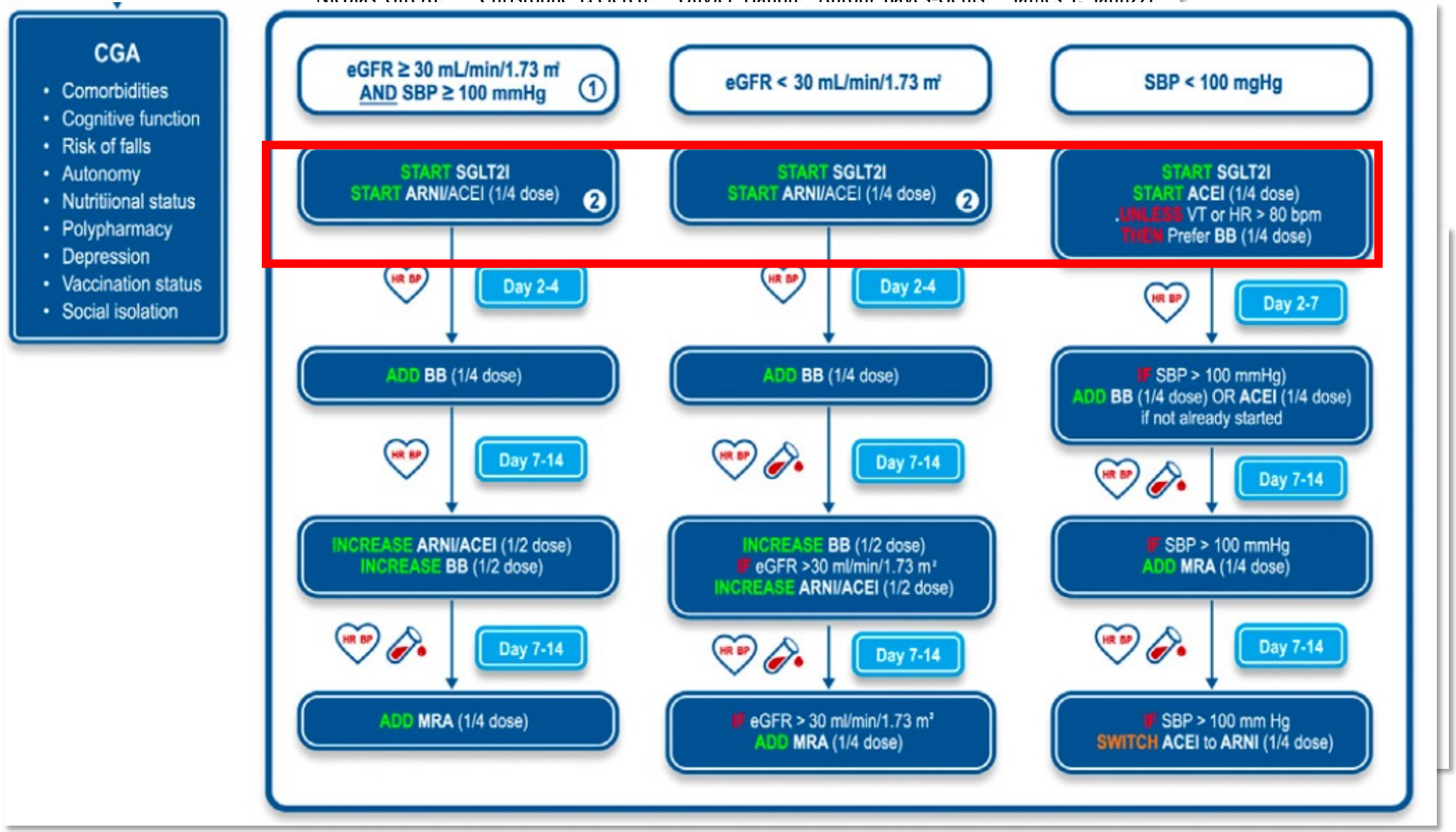
Implementar la Terapia Médica Óptima en 2-3 meses

Canadian Journal of Cardiology 37 (2021) 632–643

Special article

Optimisation of treatments for heart failure with reduced ejection fraction in routine practice: a position statement from a panel of experts

Nicolas Girerd [a,b,*] Christophe Leclercq [c,d] Olivier Hanon [e] Antoni Bayés-Genís [f,g] James L. Januzzi [h,i]



Rev Esp Cardiol. 2023. doi.org/10.1016/j.rec.2023.03.005

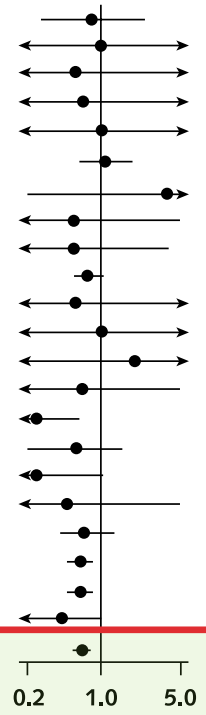
β-Blockers in Congestive Heart Failure

A Bayesian Meta-Analysis

James M. Brophy, MD, PhD; Lawrence Joseph, PhD; and Jean L. Rouleau, MD

Mortality in the placebo and β-blocker groups of 22 studies.

Study	β-Blockers, *n/n*	Placebo, *n/n*	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Anderson et al. (19)	5/25	6/25		0.80 (0.28–2.34)
Engelmeier et al. (20)	1/9	2/16		1.02 (0.08–6.84)
Pollock et al. (35)	0/12	0/7		0.60 (0.00–365)
Woodley et al. (36)	0/29	0/20		0.69 (0.00–415)
Paolisso et al. (37)	0/5	0/5		1.00 (0.00–558)
Waagstein et al. (21)	23/194	21/189		1.07 (0.61–1.88)
Wisenbaugh et al. (22)	1/11	0/13		3.86 (0.23–2697)
Fisher et al. (23)	1/25	2/25		0.58 (0.04–4.36)
Bristow et al. (24)	4/105	2/34		0.58 (0.14–3.74)
CIBIS-I (25)	53/320	67/321		0.75 (0.57–1.10)
Eichhorn et al. (26)	0/15	0/9		0.61 (0.00–373)
Metra et al. (27)	0/20	0/20		1.00 (0.00–615)
Olsen et al. (38)	1/36	0/23		1.99 (0.12–1775)
Krum et al. (39)	3/33	2/16		0.67 (0.15–4.24)
Bristow et al. (29)	12/261	13/84		0.27 (0.14–0.63)
Packer et al. (30)	6/133	11/145		0.60 (0.22–1.51)
Colucci et al. (31)	2/232	5/134		0.26 (0.04–1.04)
Cohn et al. (32)	2/70	2/35		0.49 (0.07–3.47)
Aust/NZ (28)	21/207	29/208		0.70 (0.43–1.23)
CIBIS-II (17)	156/1327	228/1320		0.64 (0.56–0.82)
MERIT-HF (18)	145/1990	217/2001		0.65 (0.55–0.82)
RESOLVD (34)	8/214	17/212		0.46 (0.20–1.02)
Total	444/5273	624/4862		0.65 (0.53–0.80)

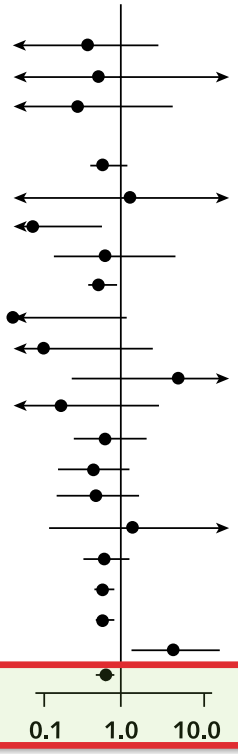


Los BB reducen la mortalidad total un 35%

Los BB reducen los ingresos por IC un 36%

Hospital admission for congestive heart failure in the placebo and β-blocker groups of 22 studies.

Study	β-Blockers, *n/n*	Placebo, *n/n*	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Anderson et al. (19)	n/a	n/a		
Engelmeier et al. (20)	1/9	4/16		0.49 (0.05–2.43)
Pollock et al. (35)	0/12	0/7		0.60 (0.00–355)
Woodley et al. (36)	1/29	2/20		0.39 (0.03–3.01)
Paolisso et al. (37)	n/a	n/a		
Waagstein et al. (21)	37/194	49/189		0.68 (0.50–1.07)
Wisenbaugh et al. (22)	0/11	0/13		1.17 (0.00–735)
Fisher et al. (23)	1/25	8/25		0.13 (0.01–0.63)
Bristow et al. (24)	7/105	3/34		0.69 (0.23–3.03)
CIBIS-I (25)	54/320	82/321		0.59 (0.48–0.90)
Eichhorn et al. (26)	0/15	2/9		0.10 (0.00–1.06)
Metra et al. (27)	0/20	2/20		0.18 (0.00–1.87)
Olsen et al. (38)	2/36	0/23		3.41 (0.34–2806)
Krum et al. (39)	1/33	2/16		0.27 (0.02–2.14)
Bristow et al. (29)	18/261	8/84		0.68 (0.34–1.68)
Packer et al. (30)	9/133	18/145		0.53 (0.25–1.14)
Colucci et al. (31)	9/232	9/134		0.56 (0.24–1.42)
Cohn et al. (32)	3/70	1/35		1.19 (0.21–17.0)
Aust/NZ (28)	23/208	33/208		0.66 (0.42–1.14)
CIBIS-II (17)	159/1327	232/1320		0.64 (0.57–0.82)
MERIT-HF (18)	200/1990	294/2001		0.65 (0.58–0.81)
RESOLVD (34)	15/214	5/212		2.93 (1.16–8.60)
Total	540/5244	754/4832		0.64 (0.53–0.79)



n = 10135. 22 Estudios. FEVI<45% BB vs placebo

Ann Intern Med. 2001;134:550-560.

Redefining β-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis

	All patients (n=15 659)	Sinus rhythm (n=12 822)	Atrial fibrillation (n=2837)
Age, years	64 (55–72)	64 (54–71)	69 (60–74)
Sex			
Women	3708 (23·7%)	3185 (24·8%)	523 (18·4%)
Men	11 951 (76·3%)	9637 (75·2%)	2314 (81·6%)
Body-mass index, kg/m²	26·6 (24·0–29·8)	26·6 (24·0–29·7)	26·9 (24·3–30·1)
Heart rate, beats per min	80 (72–88)	80 (72–88)	81 (72–92)
Systolic blood pressure, mm Hg	124 (110–140)	123 (110–139)	126 (113–140)
LVEF	27% (21–33)	27% (21–33)	27% (21–33)
Previous myocardial infarction	8538 (54·5%)	7411 (57·8%)	1127 (39·7%)
NYHA class III or IV	8802 (63·7%)	7048 (61·9%)	1754 (72·6%)
Creatinine, µmol/L	105 (88–124)	104 (88–124)	108 (90–131)
ACEi or ARB	14 877 (95·0%)	12 188 (95·1%)	2689 (94·8%)
Any diuretic therapy	13 563 (86·6%)	10 914 (85·1%)	2649 (93·4%)
Anticoagulation therapy	5033 (32·1%)	3379 (26·4%)	1654 (58·3%)
Digoxin	9299 (59·4%)	6919 (54·0%)	2380 (83·9%)

Data are median (IQR) or n (%). Breakdown according to randomised treatment allocation (β blockers *vs* placebo) is provided in the appendix (p 8). ACEi=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association.

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Los BB en IC-FEr reducen la mortalidad en RS pero no en FA

	Annualised mortality	Placebo	β blockers	Odds ratio (95% CI)	Risk ratio (95% CI)	p value	Number needed to treat (95% CI)
SR							
SR all	15·8%	1121/6276 (17·9%)	907/6546 (13·9%)	0·74 (0·67–0·81)	0·86 (0·81–0·90)	<0·0001	25 (18–39)
SR1	3·9%	14/222 (6·3%)	8/211 (3·8%)	0·59 (0·24–1·43)	0·74 (0·41–1·29)	0·23	NA
SR2	5·7%	40/487 (8·2%)	34/514 (6·6%)	0·79 (0·49–1·27)	0·89 (0·69–1·14)	0·33	NA
SR3	9·1%	108/731 (14·8%)	59/683 (8·6%)	0·54 (0·39–0·76)	0·71 (0·57–0·87)	0·0004	16 (11–36)
SR4	8·8%	151/1231 (12·3%)	140/1306 (10·7%)	0·86 (0·67–1·10)	0·93 (0·82–1·05)	0·22	NA
SR5	10·3%	267/1706 (15·7%)	202/1791 (11·3%)	0·69 (0·56–0·83)	0·82 (0·74–0·92)	0·0001	23 (15–47)
SR6	19·6%	541/1899 (28·5%)	464/2041 (22·7%)	0·74 (0·64–0·85)	0·86 (0·80–0·93)	<0·0001	17 (12–33)
AF							
AF all	20·4%	300/1425 (21·1%)	278/1412 (19·7%)	0·92 (0·77–1·10)	0·96 (0·87–1·05)	0·37	NA
AF1	13·8%	50/307 (16·3%)	59/301 (19·6%)	1·25 (0·83–1·90)	1·12 (0·92–1·36)	0·29	NA
AF2	9·2%	50/338 (14·8%)	29/321 (9·0%)	0·57 (0·35–0·93)	0·73 (0·54–0·98)	0·023	17 (9–119)
AF3	15·1%	68/348 (19·5%)	69/348 (19·8%)	1·02 (0·70–1·48)	1·00 (0·84–1·22)	0·92	NA
AF4	28·4%	81/201 (40·3%)	68/202 (33·7%)	0·75 (0·50–1·13)	0·87 (0·70–1·07)	0·17	NA
AF5	17·0%	51/231 (22·1%)	53/240 (22·1%)	1·00 (0·65–1·55)	1·00 (0·81–1·24)	1·0	NA

Data are % or n/N (%), unless stated otherwise. Results are based on objective assessment for the number of dimensions and clusters for sinus and atrial fibrillation, as defined by the gap statistic. NA=not applicable as the absolute risk reduction with β blockers is not significant. SR=sinus rhythm. AF=atrial fibrillation.

An individual patient data (IPD) meta-analysis of all major beta-blocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF with AF.[125] However, since this is a retrospective subgroup analysis, and because beta-blockers did not increase risk, the guideline committee decided not to make a separate recommendation according to heart rhythm.

McDonagh, et al. *European Heart Journal.* 2021;1-128. https://doi.org/10.1093/eurheartj/ehab368

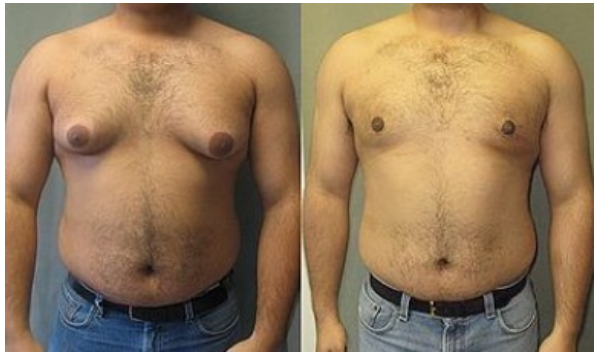
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2011 VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

NNT 13



The New England Journal of Medicine

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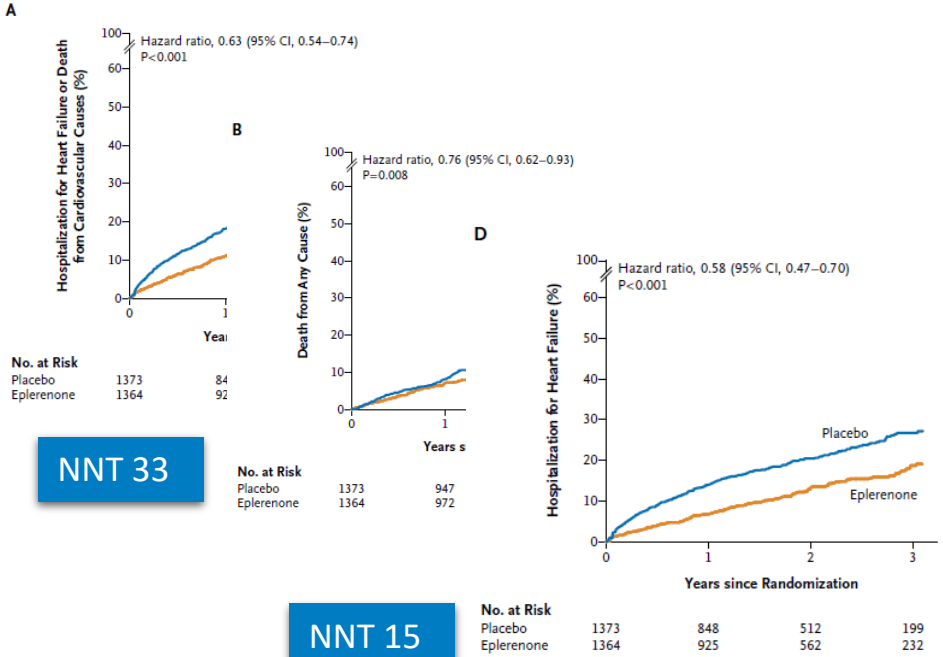
VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

NNT 33



NNT 15

NNT 8

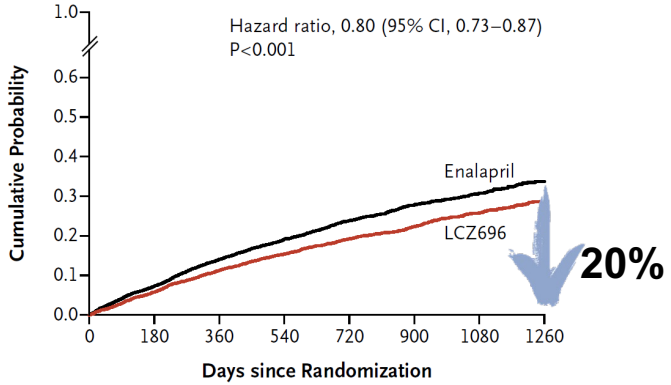
NNT 14

NNT 10

VARIABLE	PLACEBO GROUP (N=841)	SPIRONOLACTONE GROUP (N=822)	RELATIVE RISK (95% CI)*	P VALUE
	no. of patients			
Cause of death				
Cardiac causes	314	226	0.69 (0.58–0.82)	<0.001
Progression of heart failure†	189	127	0.64 (0.51–0.80)	<0.001
Sudden death‡	110	82	0.71 (0.54–0.95)	0.02
Total	386	284	0.70 (0.60–0.82)	<0.001
Reason for hospitalization				
Cardiac causes§	336/753	260/515	0.70 (0.59–0.82)	<0.001
Worsening heart failure	300/663	215/413	0.65 (0.54–0.77)	<0.001

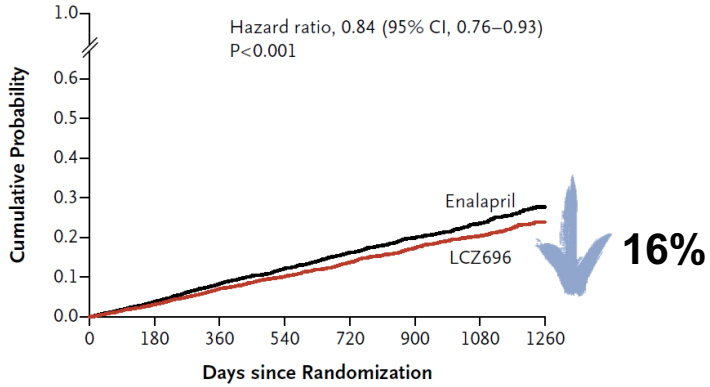
Estudio PARADIGM-HF

Endpoint primario. Mortalidad Cardiovascular u hospitalización por IC



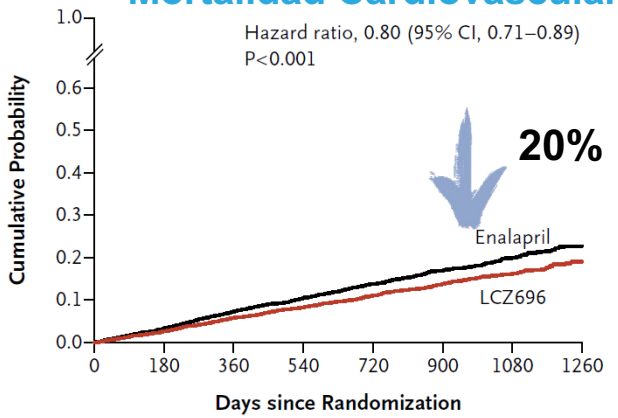
No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Mortalidad por todas las causas



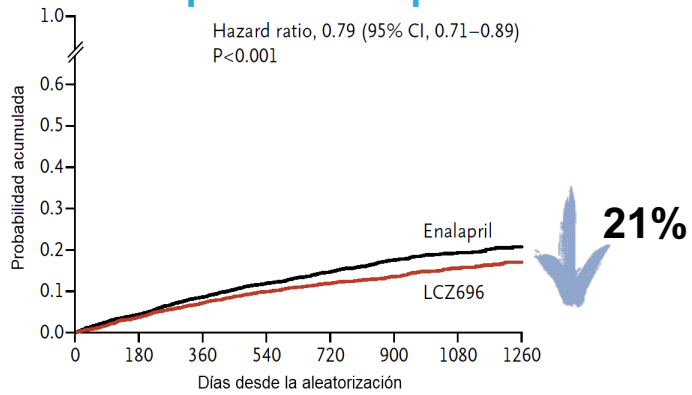
No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

Mortalidad Cardiovascular



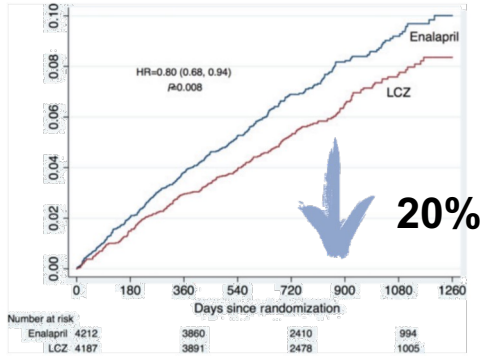
No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

Hospitalización por IC

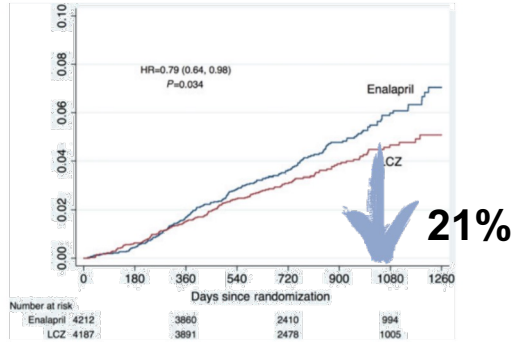


Nº en riesgo								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

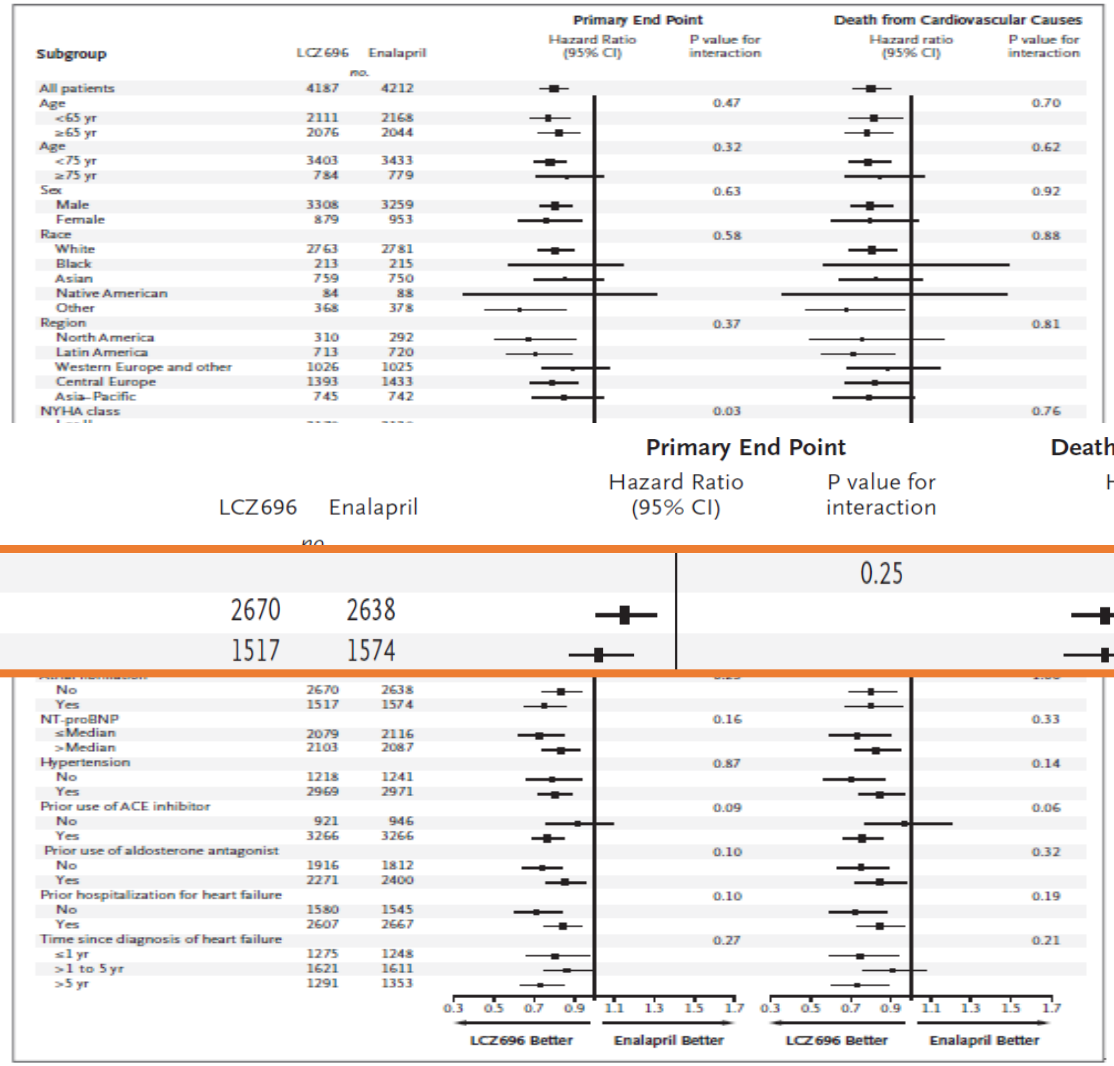
Muerte súbita



Muerte por empeoramiento de la IC



McMurray J *et al*. N Engl J Med. 2014; 371:993-1004



Primary End Point
Death from Cardiovascular Causes
Subgroup
LCZ696
Enalapril
Hazard Ratio (95% CI)
P value for interaction
Hazard ratio (95% CI)
P value for interaction
Atrial fibrillation 0.25 1.00
No 2670 2638
Yes 1517 1574

McMurray, et al. N Engl J Med. 2014;371(11):993-1004

PIONEER-HF: Resultados

Objetivo clínico combinado exploratorio grave

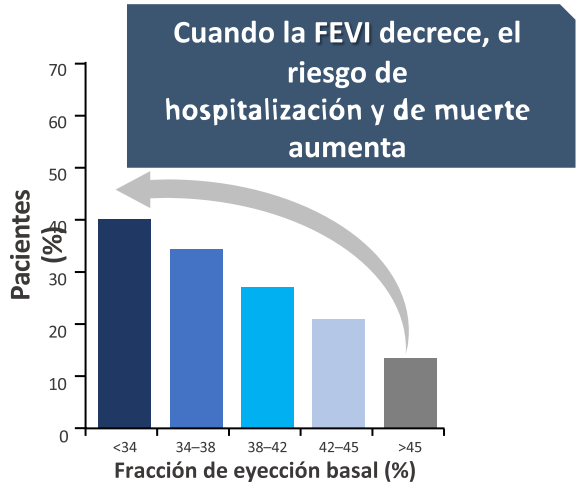
Muerte, hospitalización por IC, o necesidad de DAVI, Tx

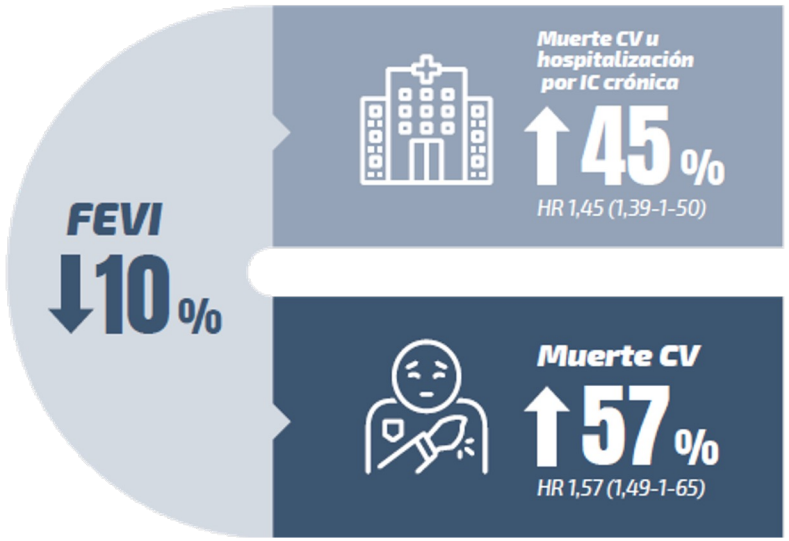
Eventos de seguridad (%)	Sacubitrilo/Valsartán (n=440)	Enalapril (n=441)	RR (95% IC)
Empeoramiento de la función renal*	13.6	14.7	0.93 (0.67-1.28)
Hiperpotasemia†	11.6	9.3	1.25 (0.84-1.84)
Hipotensión sintomática	15.0	12.7	1.18 (0.85-1.64)
Evento de angioedema	1 (0.2%)	6 (1.4%)	0.17 (0.02-1.38)

- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF re-hospitalizations

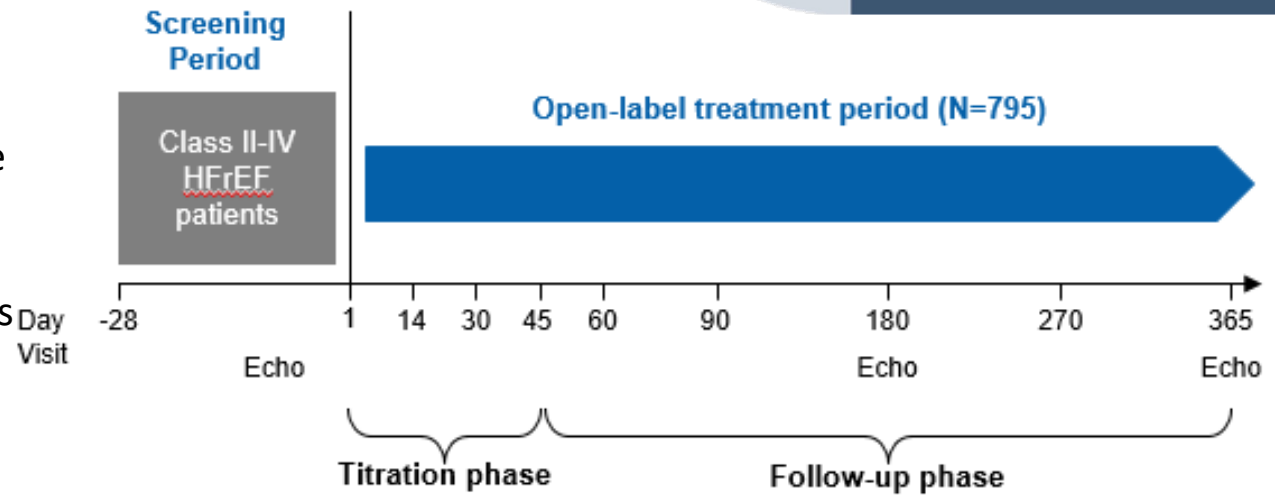
Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

Estudio PROVE-HF. Efecto del Sac/Val en biomarcadores, remodelado miocárdico y outcomes





- LVEF ≤40%
- Stable dose of loop diuretic for the 2 weeks preceding study start



PROVE-HF

- **Objetivo primario.** Correlación entre los valores de NT-proBNP y remodelado a los 12 meses: LVEF, LVEDVi, LVESVi, LAVi, E/e'
- **Objetivo secundario.**

- Asociación entre el cambio de NT-proBNP y el remodelado a los 6 meses

- Efecto del S/V en el remodelado cardiaco en grupos predefinidos en el PARADIGM-HF trial:

IC de novo y/o naïve para ACEI/ARB

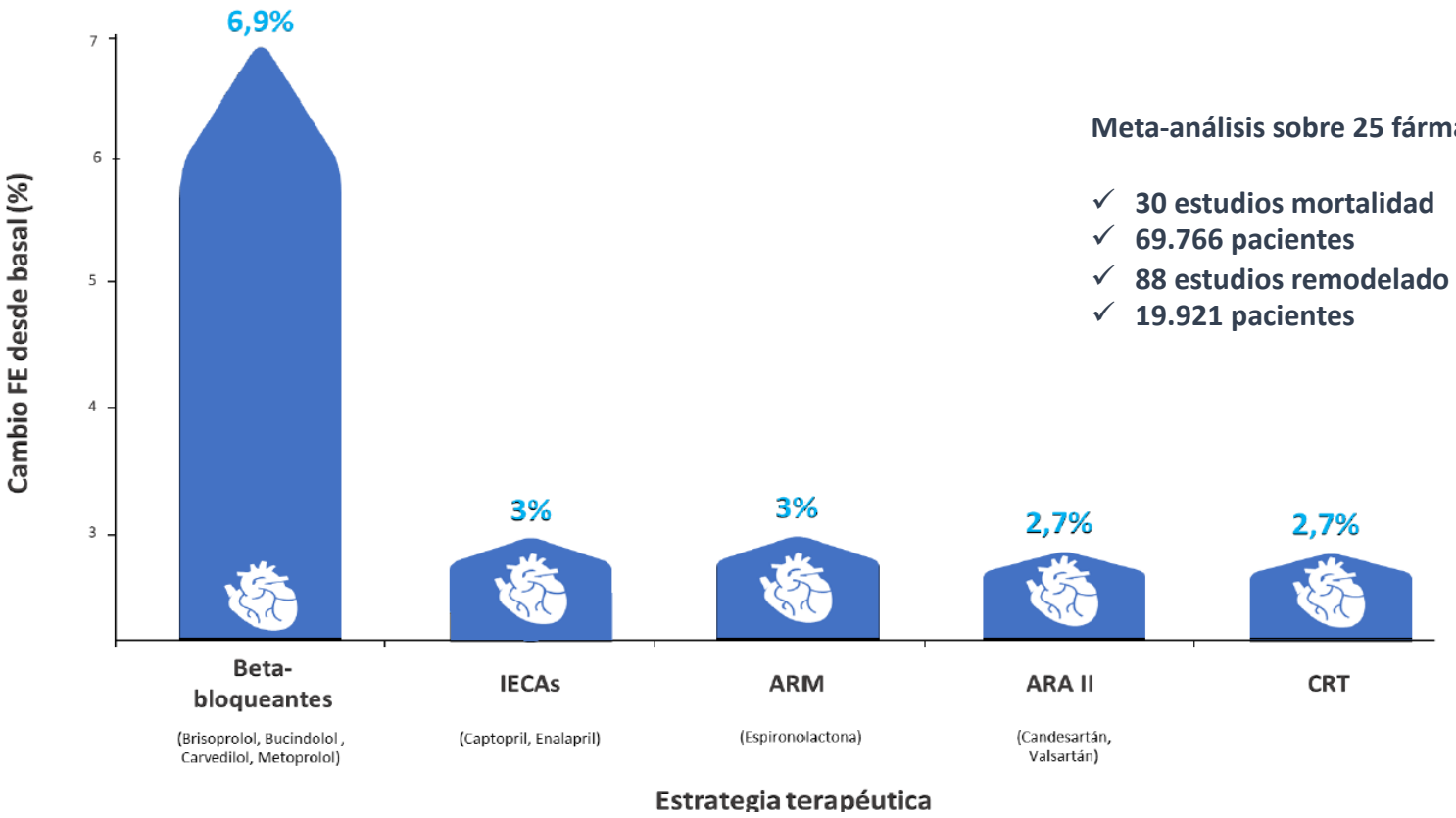
Aquellos pacientes con concentraciones de **BNP or NT-proBNP por debajo de los criterios de inclusión de PARADIGM-HF**

Pacientes que **no alcanzan dosis objetivo** de S/V (97/103 mg/12h a diario)

LVEF Left ventricular ejection fraction; *LVEDVi* LV end-diastolic volume index; *LVESVi* LV end-systolic volume index; *LAVi* Left atrial volume index; *E/e'* Ratio of early mitral diastolic filling velocity/early diastolic mitral annular velocity. Januzzi, JAMA. 2019

Contexto previo: *Meta-análisis Kramer (2010, JACC)*

Cambios absolutos en la FEVI con tratamiento farmacológico o dispositivos vs placebo



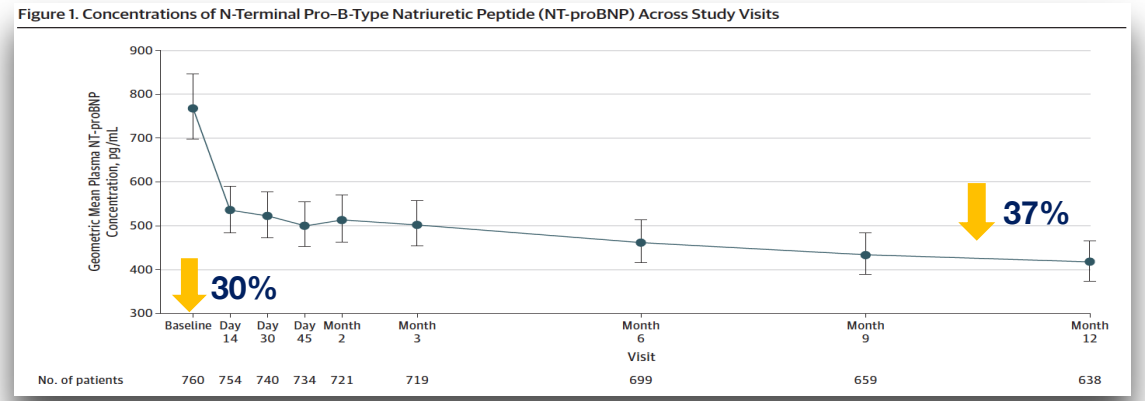
Meta-análisis sobre 25 fármacos/dispositivos en IC:

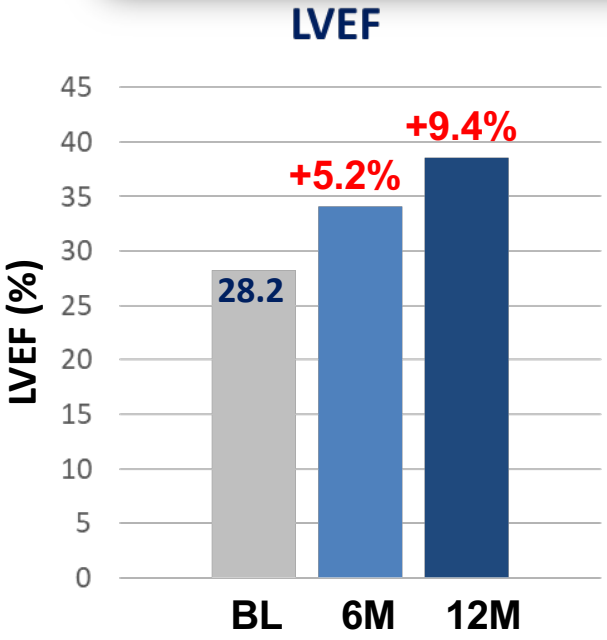
- ✓ **30 estudios mortalidad**
- ✓ **69.766 pacientes**
- ✓ **88 estudios remodelado**
- ✓ **19.921 pacientes**

adaptado de Kramer DG et al. JACC 2010

Estudio PROVE-HF. Remodelado adverso cardiaco

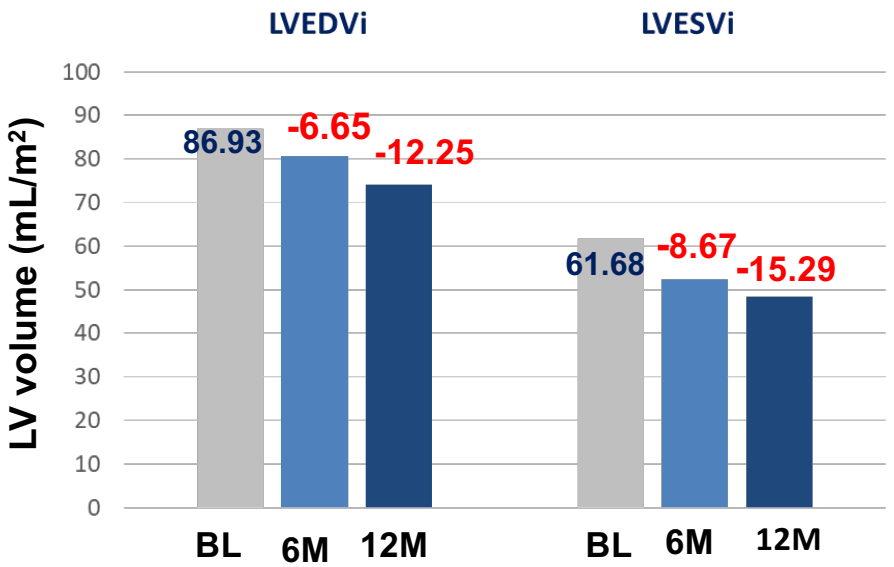
PROVE-HF

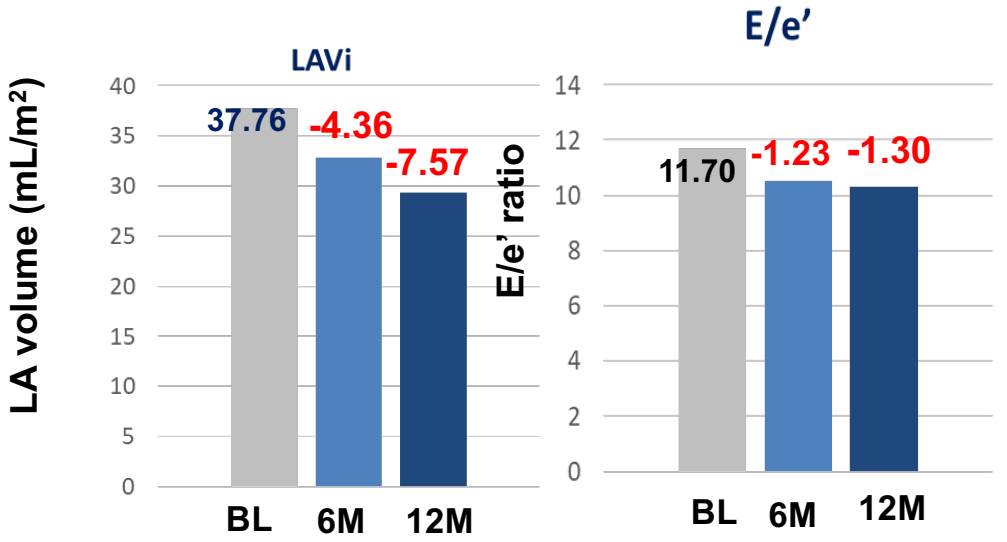




25% de los pacientes experimentaron un incremento en LVEF ≥13% a los 12 meses

Baseline to 12 months: all P <0.001





La masa del VI indexada se redujo de 124,77 a 107,82 g/m² (media -16,00 g/m²; *p* <0,001)

BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; M, months. Januzzi *et al*, Prospective Study of Biomarkers and Ventricular Remodeling During Entresto Therapy for Heart Failure.

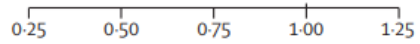
SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer

B Cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	187/1863 (10·0%)	202/1867 (10·8%)	0·92 (0·75–1·12)
DAPA-HF	227/2373 (9·6%)	273/2371 (11·5%)	0·82 (0·69–0·98)
Total			**0·86 (0·76–0·98)**

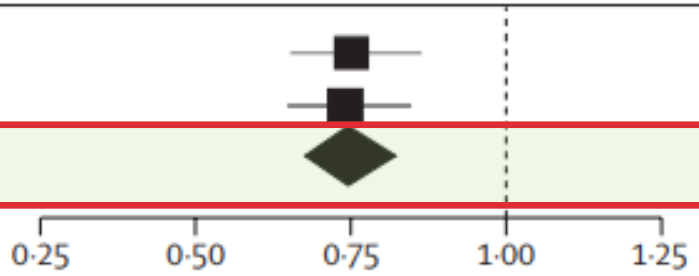
Test for overall treatment effect p=0·027
Test for heterogeneity of effect p=0·40



C First hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
DAPA-HF	386/2373 (16·3%)	502/2371 (21·2%)	0·74 (0·65–0·85)
Total			**0·74 (0·68–0·82)**

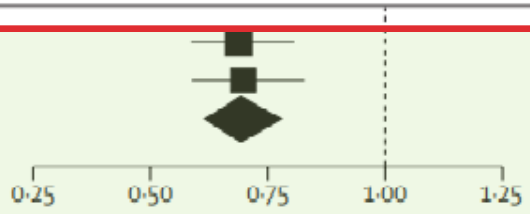
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·89



D First hospitalisation for heart failure

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	246/1863 (13·2%)	342/1867 (18·3%)	0·69 (0·59–0·81)
DAPA-HF	231/2373 (9·7%)	318/2371 (13·4%)	0·70 (0·59–0·83)
Total			**0·69 (0·62–0·78)**

Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·90



F. Zannad, et al.SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet;396(10254):819-829. DOI: 10.1016/S0140-6736(20)31824-9

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 671–680
doi:10.1093/eurheartj/ehaa968
FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

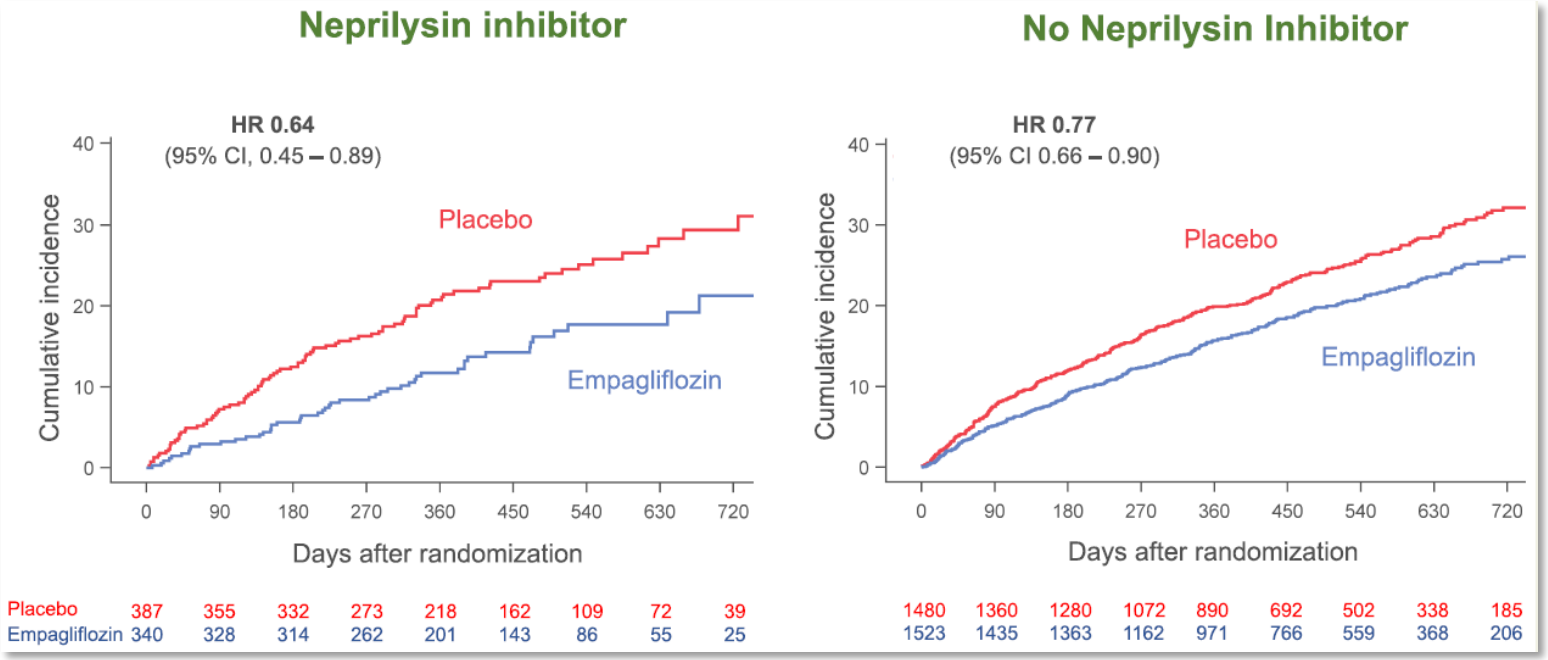
Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial

El efecto de empagliflocina sobre la mortalidad CV e ingresos por IC es un 13% mayor en los tratados con SAC/VAL

- Reducción del riesgo de mortalidad CV o ingresos por IC
  - Empagliflocina solo: 23%
  - Empagliflocina junto a SAC/VALS : **36%**

Table 2 Effects of empagliflozin in patients taking and not taking a neprilysin inhibitor at baseline

	Patients not taking a neprilysin inhibitor ($n = 3003$)		Patients taking a neprilysin inhibitor ($n = 727$)		Interaction *P*-value
	Placebo ($n = 1480$)	Empagliflozin ($n = 1523$)	Placebo ($n = 387$)	Empagliflozin ($n = 340$)	
Cardiovascular death or adjudicated hospitalization for heart failure [*n* (%)]	369 (24.9)	310 (20.9)	93 (24.0)	51 (15.0)	0.31
	HR 0.77 (0.66–0.90)		HR 0.64 (0.45–0.89)		
	$P = 0.0008$		$P = 0.0094$		



points is shown in *Table 2*. When compared with placebo, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure by 23% in the patients not taking a neprilysin inhibitor and by 36% in the patients taking a neprilysin inhibitor, hazard ratios of 0.77 (95% CI 0.66–0.90), $P = 0.0008$ and 0.64 (95% CI 0.45–0.89), $P = 0.009$, respectively. Empagliflozin decreased the total

European Heart Journal (2021) **42**, 671–680
doi:10.1093/eurheartj/ehaa968

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FASTTRACK CLINICAL RESEARCH
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Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial

El efecto de empagliflocina sobre la mortalidad CV es un 22% mayor en los tratados con SAC/VAL

- Reducción del Riesgo de Mortalidad CV:
  - Emagliflocina solo: 5%
  - Empagliflocina junto a SAC/VALS: **27%**

the interaction *P*-values were >0.05 (*Table 2*). When compared with placebo, empagliflozin reduced the risk of cardiovascular death by 5% in the patients not taking a neprilysin inhibitor and by 27% in the patients taking a neprilysin inhibitor, hazard ratios of 0.95 (95% CI 0.76–1.18) and 0.73 (95% CI 0.42–1.25), respectively. Empagliflozin

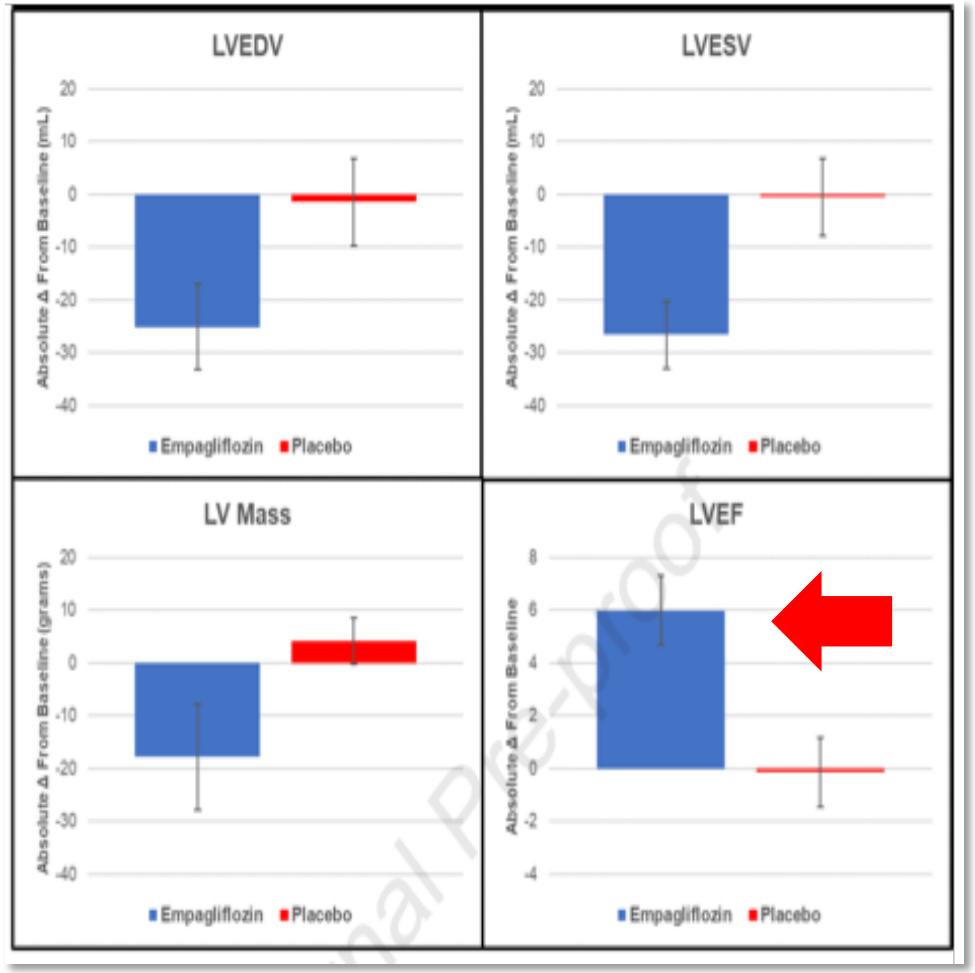
European Heart Journal (2021) **42**, 671–680
doi:10.1093/eurheartj/ehaa968

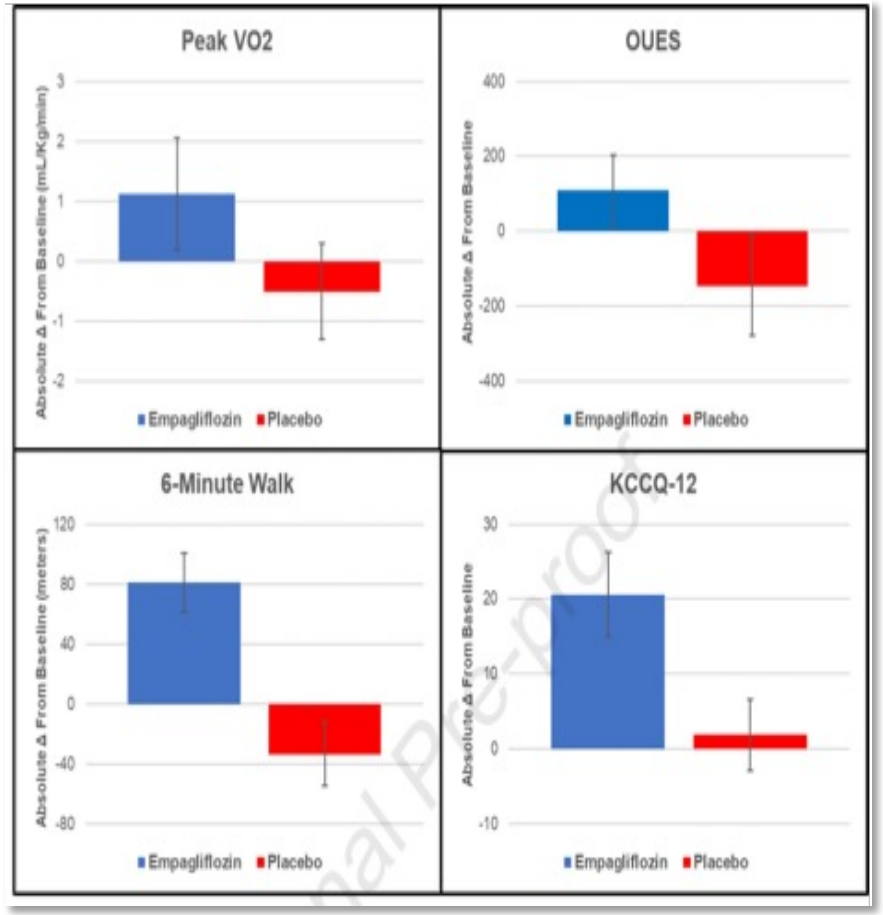
Journal Pre-proof

JACC

Randomized Trial of Empagliflozin in Non-Diabetic Patients with Heart Failure and Reduced Ejection Fraction

EMPATROPISM



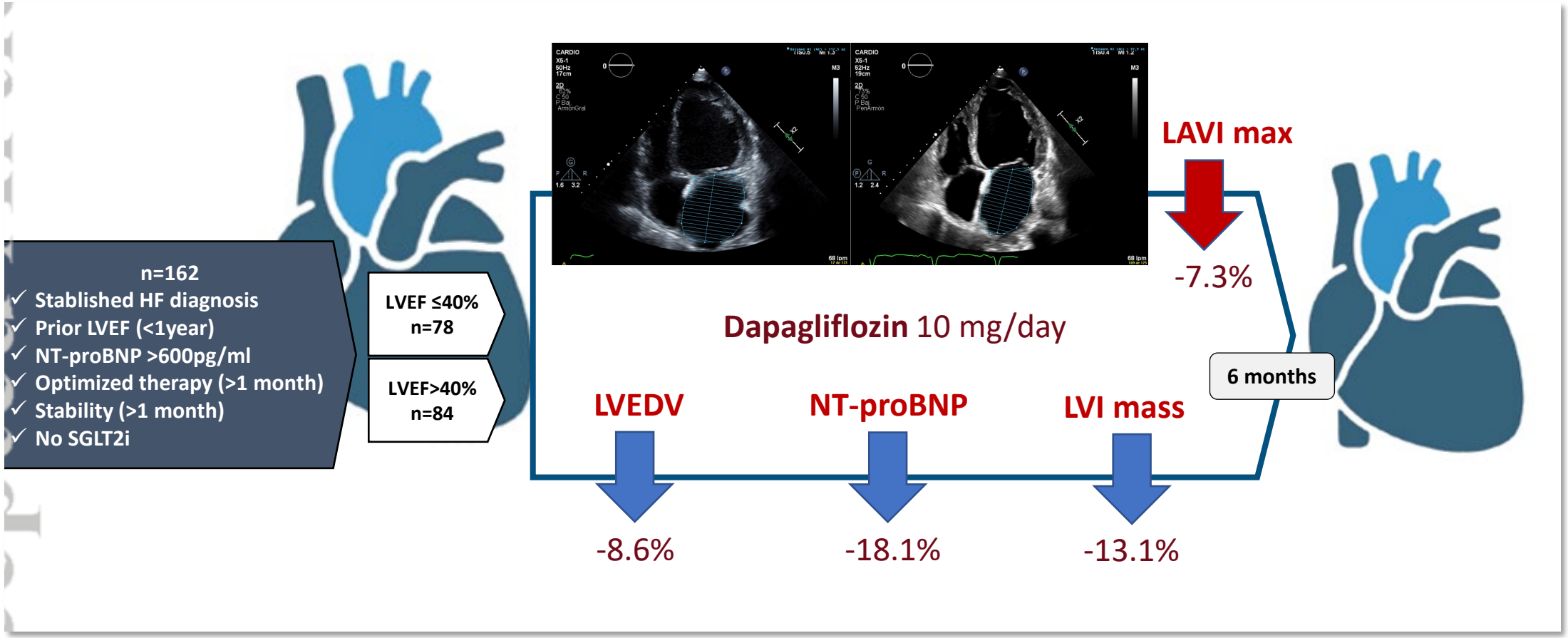


- **N= 84** No Diabéticos
- **FEVi< 50%**
- **Pacientes estables con TMO los últimos 3 meses.**
- BB 88%/**ARNI 43%/**IECAs ó ARA 42%.
- Seguidos **6 meses**
- **LVEDVI -25.1ml.**
- **LVESVI -25.6 ml**
- **FEVi +6%**
- VO2 max +1.1 ml/min/kg.
- 6MWalkTest +81m
- KCCQ +21

https://doi.org/10.1016/j.jacc.2020.11.008

Impact of Dapagliflozin on cardiac remodeling in patients with chronic heart failure: DAPA-MODA study.

DA. Pascual-Figal[1,2,3,4], JL. Zamorano[4,5], M. Domingo[6], H. Morillas[7], J. Nuñez[8], M. Cobo Marcos[9], A. Riquelme-Pérez[2,4], Albert Teis[6], E. Santas[8], C. Caro[1], JM. Pinilla[10], JF. Rodriguez-Palomares[4,11], D. Dobarro[12], MA. Restrepo-Córdoba[13], JR. González-Juanatey[14], A. Bayés Genís[4,6] on behalf of DAPA-MODA study investigators (see appendix)



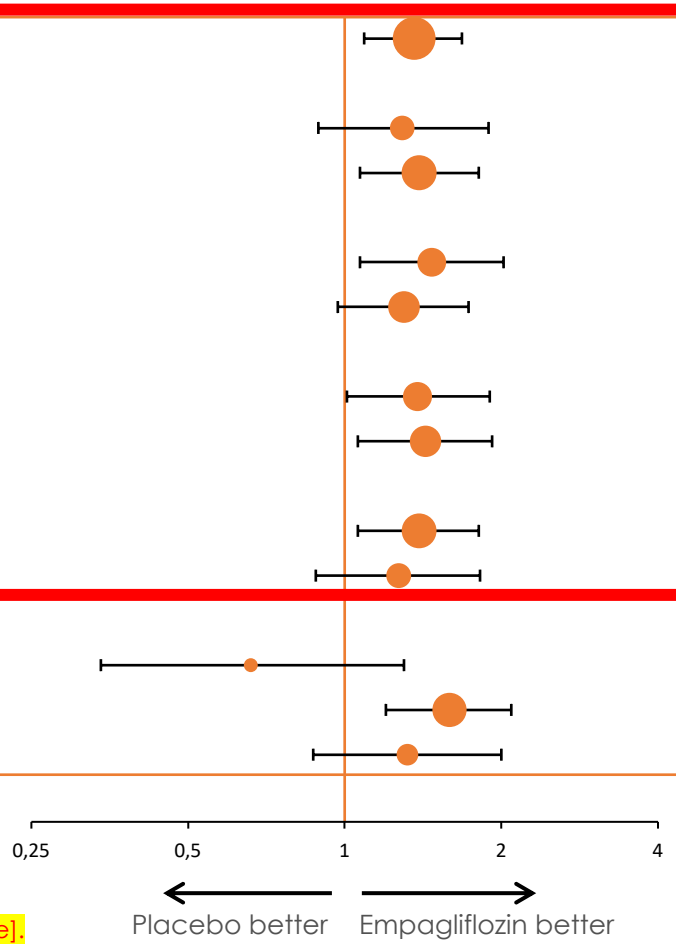
10.1002/ejhf.2884

PIONEERHF		EMPULSE
24h-10d	Randomización	24h-5 d
> 100mmHg (6h)		> 100mmHg (6h)
No aumento iv 6h	Diurético iv	No aumento iv 6h
No 24h	inotrópico	No 24h
FEVI< 40%		ICr/ICm/ICp
NT-proBNP ≥1600 pg/mL o BNP ≥400 pg/mL	proBNP	NT-proBNP ≥1600 pg/mL o BNP ≥400 o 72h previa NT-proBNP ≥2400 pg/mL o BNP ≥600 pg/mL FA

EMPULSE:Primary endpoint subgroup analysis (1 of 2)

Significación estadística desde el día 15

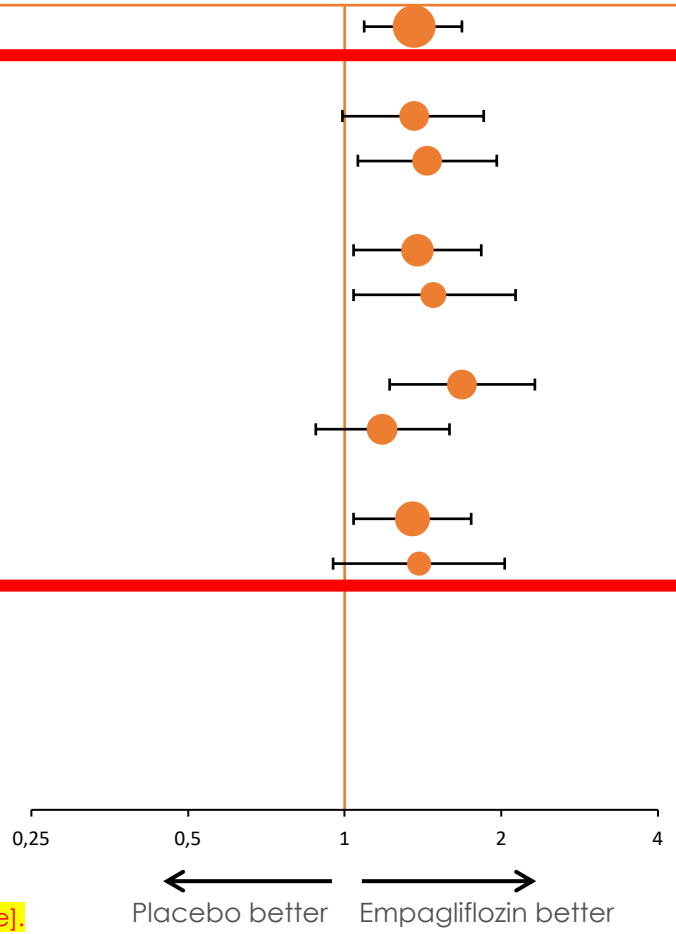
	Empagliflozin n with event/total N	Placebo n with event/total N	Win ratio (95% CI)	Interaction *p*-value
All patients	265	265	1.36 (1.09, 1.68)	
HF status				0.7590
De novo	88	87	1.29 (0.89, 1.89)	
Decompensated chronic	177	178	1.39 (1.07, 1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07, 2.02)	
Non-diabetic	141	149	1.30 (0.97, 1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01, 1.90)	
≥70 years	149	136	1.43 (1.06, 1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06, 1.81)	
Female	86	93	1.27 (0.88, 1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34, 1.30)	
Europe	168	171	1.59 (1.20, 2.09)	
North America	66	69	1.32 (0.87, 2.00)	



CI, confidence interval; HF, heart failure.
Voors AA *et al.* AHA 2021; oral presentation XXXX [please update when available].

EMPULSE: Primary endpoint subgroup analysis (2 of 2)

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	n with event/total N			
All patients	265	265	1.36 (1.09, 1.68)	
NT-proBNP at baseline, pg/mL				0.7904
<Median	125	130	1.36 (0.99, 1.85)	
≥Median	130	126	1.44 (1.06, 1.96)	
eGFR (CKD-EPI) at baseline, mL/min/1.73 m^2				0.7562
<60	161	145	1.38 (1.04, 1.83)	
≥60	88	106	1.48 (1.04, 2.13)	
Atrial fibrillation/flutter at baseline				0.1129
No	123	133	1.68 (1.22, 2.32)	
Yes	142	132	1.18 (0.88, 1.59)	
Baseline LVEF, %				0.9008
≤40	182	172	1.35 (1.04, 1.75)	
>40	76	92	1.39 (0.95, 2.03)	



CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Voors AA *et al.* AHA 2021; oral presentation XXXX [please update when available].

ON MY MIND

Victims of Success in Failure

Carolyn S.P. Lam, MBBS, PhD
Javed Butler, MD, MPH, MBA

Principles and Pathophysiologic Targets of HFrEF Pharmacotherapy

6 PATHWAYS

Modulation of five pathways shown to improve outcomes in the general HFrEF population

Angiotensin 2

Norepinephrine

Aldosterone

Neprilysin

SGLT

NO–sGC–cGMP

4 DRUGS

ARNI

May start with ACEi/ARB or ARNI in de novo. May use ACEi/ARB if cost or availability concerns.

Beta-blockers

Carvedilol, bisoprolol, metoprolol succinate

MRAs

SGLT2i

Dapagliflozin, Empagliflozin

3 OTHERS

Three additional pathways shown to improve outcomes in specific populations:

Ivabradine

NSR HR≥70 bpm

Hydralazine/nitrate

Self identified blacks

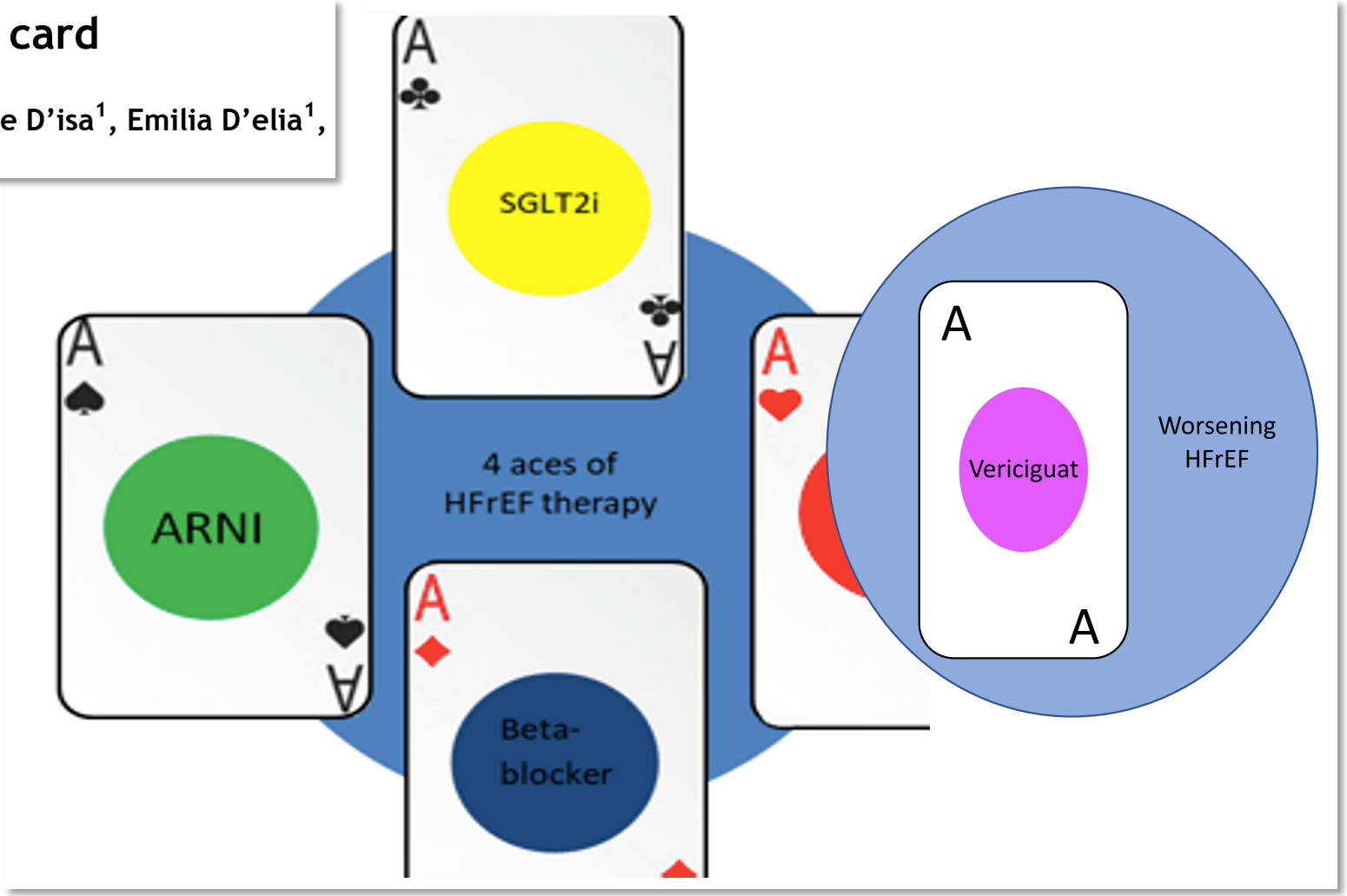
Vericiguat

Worsening HF

Circulation. 2020;142:1129–1131. DOI: 10.1161/CIRCULATIONAHA.120.048365

Heart failure therapy: the fifth card

Giulio Balestrieri[1], Edoardo Sciatti[1], Salvatore D'isa[1], Emilia D'elia[1], and Michele Senni[1,2]



European Heart Journal Supplements (2023) **25** (Supplement B), B140–B143 *The Heart of the Matter*
https://doi.org/10.1093/eurheartjsupp/suad099

Las características iniciales reflejan la población de pacientes de alto riesgo incluidos en VICTORIA

Características basales	VICTORIA (N = 5050)
Edad, años, media ± DE	67,3 ± 12,2
Sexo, mujer, *n* (%)	1.208 (23,9)
Raza, *n* (%)	
Caucásicos	3239 (64,1)
Asiáticos	1132 (22,4)
Afroamericanos	249 (4,9)
Otros	430 (8,5)
Región geográfica, *n* (%)	
Europa Oriental	1694 (33,5)
Europa Occidental	889 (17,6)
Asía-Pacífico	1183 (23,4)
América Latina	724 (14,3)
Norteamérica	560 (11,1)
Evento índice, *n* (%)	
Hospitalización por IC en los 3 meses previos	3378 (66,9)
Hospitalización por IC entre los 3 y 6 meses previos	871 (17,2)
Diurético IV por IC (sin hospitalización) en los 3 meses previos	801 (15,9)

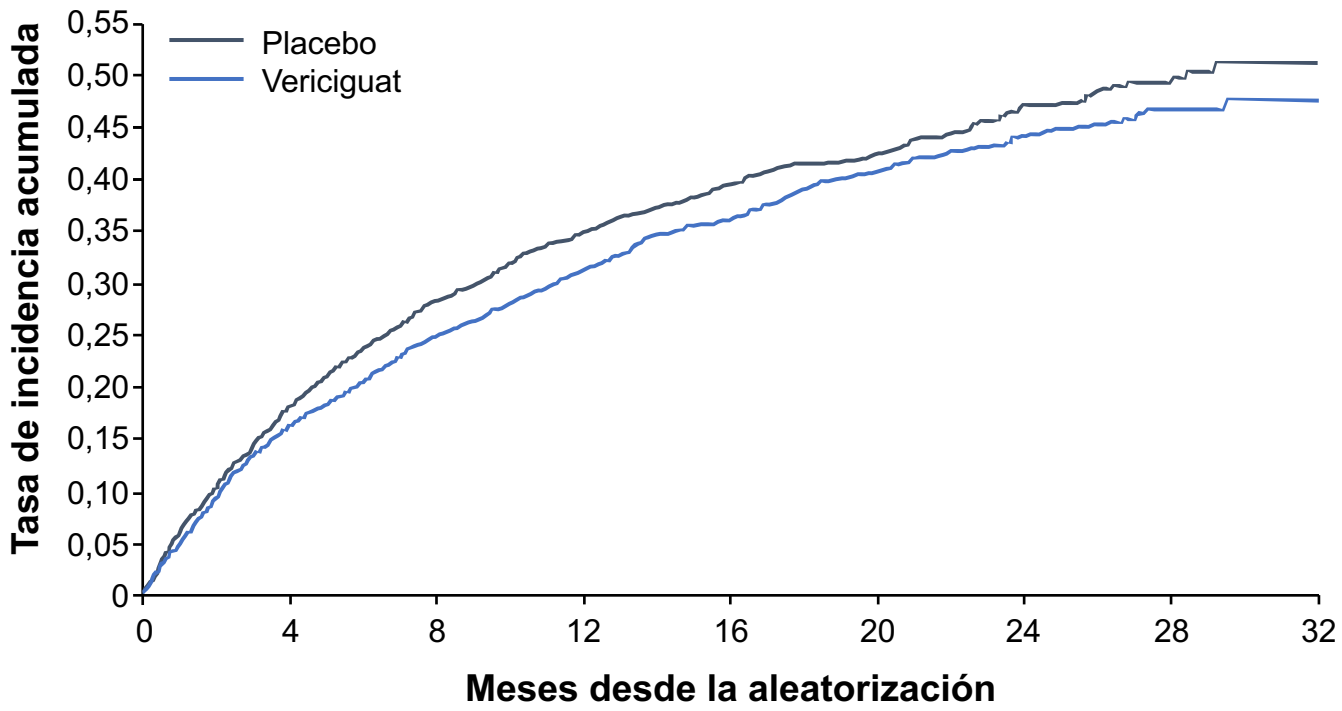
Características basales	VICTORIA (N = 5050)
FE en la selección, %, media ± DE	28,9 ± 8,3
Clase de la NYHA al inicio, *n* (%)	
n	5046
II	2975 (59,0)
III	2003 (39,7)
IV	66 (1,3)
Categoría de TFGe en la aleatorización, ml/min/1,73 m^2, *n* (%)	
n	4959
≤30	506 (10,2)
>30 a ≤60	2118 (42,7)
>60	2335 (47,1)
NT-proBNP en la aleatorización, pg/ml	
n	4805
Mediana (percentil 25-75)	2816,0 (1556,0-5314,0)
Triple terapia, *n/N* (%)	3009/5040 (59,7 %)
DAI, *n/N* (%)	1399/5040 (27,8 %)
Marcapasos biventricular, *n/N* (%)	739/5040 (14,7 %)

FE: fracción de eyección; TFGe: tasa de filtrado glomerular estimada; IC: insuficiencia cardiaca; DAI: desfibrilador automático implantable; IV: intravenoso; NT-proBNP: péptido natriurético de tipo N-terminal pro-B; NYHA: New York Heart Association; DE: desviación estándar.

Referencias bibliográficas: Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893.

Vericiguat redujo significativamente los episodios del criterio principal de valoración compuesto de primera hospitalización por IC o muerte por causas CV

- **Tiempo transcurrido hasta la primera hospitalización por IC o muerte por causas CV**



Número de pacientes en riesgo

Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

Mediana de la duración del tratamiento para el criterio principal de valoración: 10,8 meses

Tasa anual de episodios por 100 pac/año:

Vericiguat	33,6
Placebo	37,8

HR=0,90 (IC del 95 % 0,82-0,98); p=0,02

RAR 4,2 episodios/100 pac/año

NNT anual = 24*

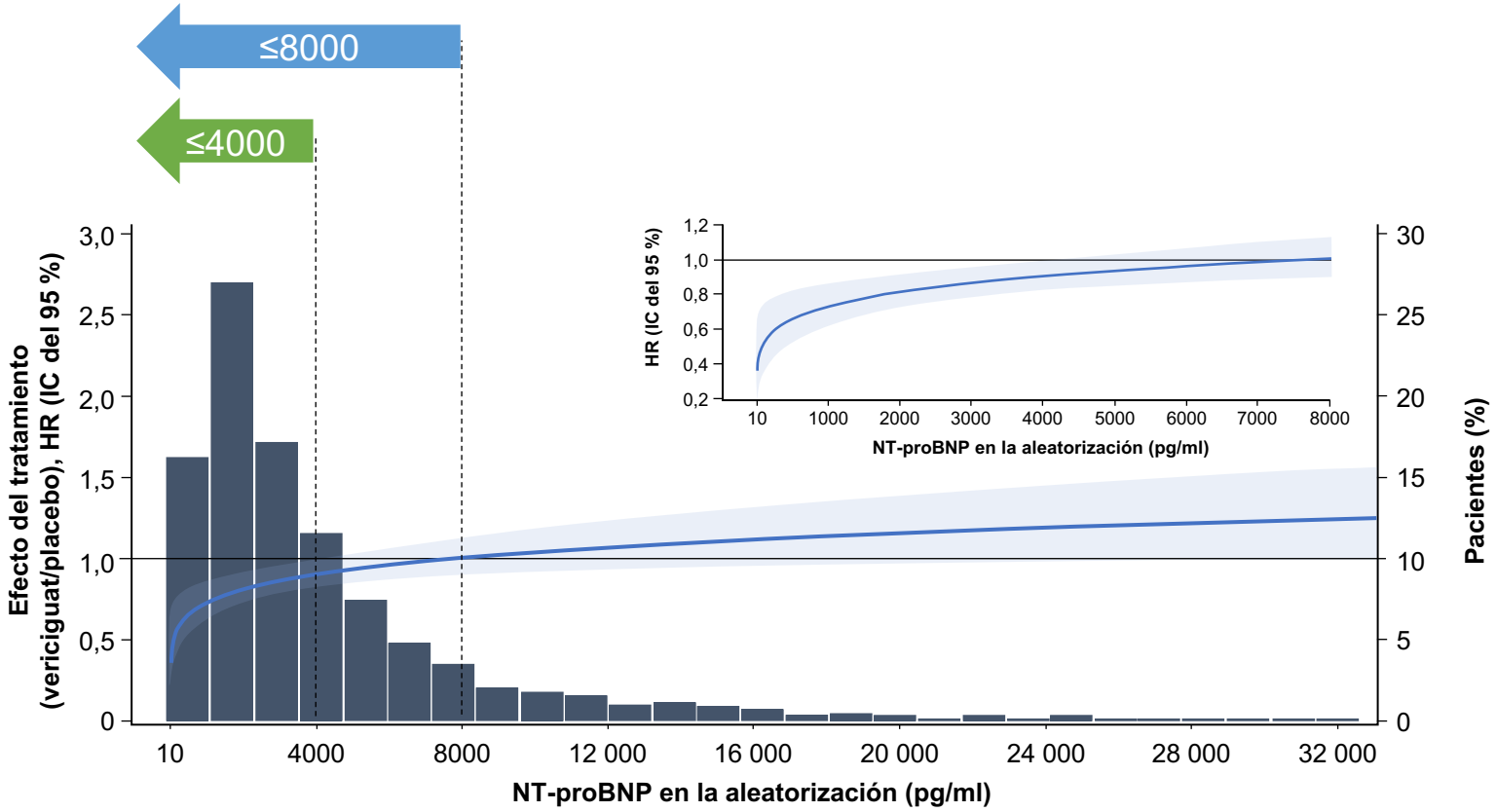
* Cálculos: NNT anual = 100/4,2 = 24.

RAR: reducción absoluta del riesgo; IC: intervalo de confianza; CV: cardiovascular; IC: insuficiencia cardíaca; HR: cociente de riesgos instantáneos; NNT: número de pacientes necesario a tratar durante 1 año para evitar un evento; pac/año: pacientes/año.

Referencias bibliográficas: Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893.

El beneficio de vericiguat se conservó en pacientes con niveles de NT-proBNP de hasta 8000 pg/ml[1,2]

- **Efecto del tratamiento con vericiguat sobre el criterio principal de valoración por el NT-proBNP en la aleatorización[1]**



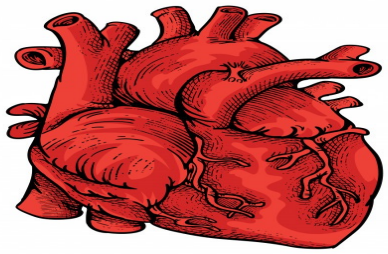
El efecto positivo del tratamiento con vericiguat en comparación con el placebo en el criterio principal de valoración fue:

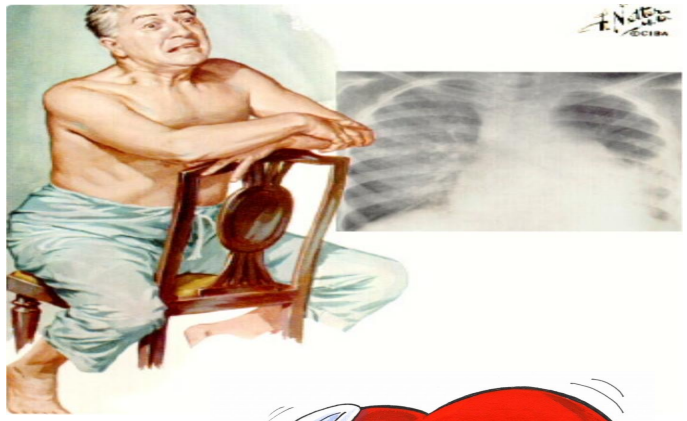
- Evidente para pacientes con **NT-proBNP ≤8000 pg/ml** (86 % de la población de VICTORIA)[1]
- Amplificado aún más en pacientes con **NT-proBNP ≤4000 pg/ml** (65 % de la población de VICTORIA)[1]

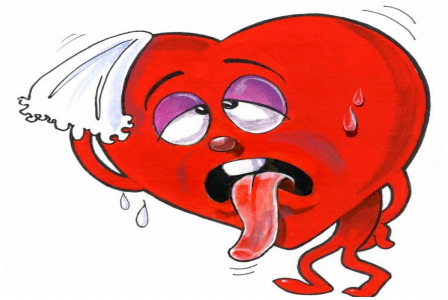
Intervalo del efecto del tratamiento con vericiguat en comparación con el placebo para el criterio principal de valoración compuesto por el NT-proBNP en la aleatorización, ajustado por la puntuación de riesgo MAGGIC.
IC: intervalo de confianza; HR: cociente de riesgos instantáneos; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure; NT-proBNP: péptido natriurético de tipo N-terminal pro-B.

Referencias bibliográficas: 1. Ezekowitz JA *et al. JACC Heart Fail* 2020;8:931–939;

ACTUALIZACIÓN EN EL TRATAMIENTO DE LA ICFEp

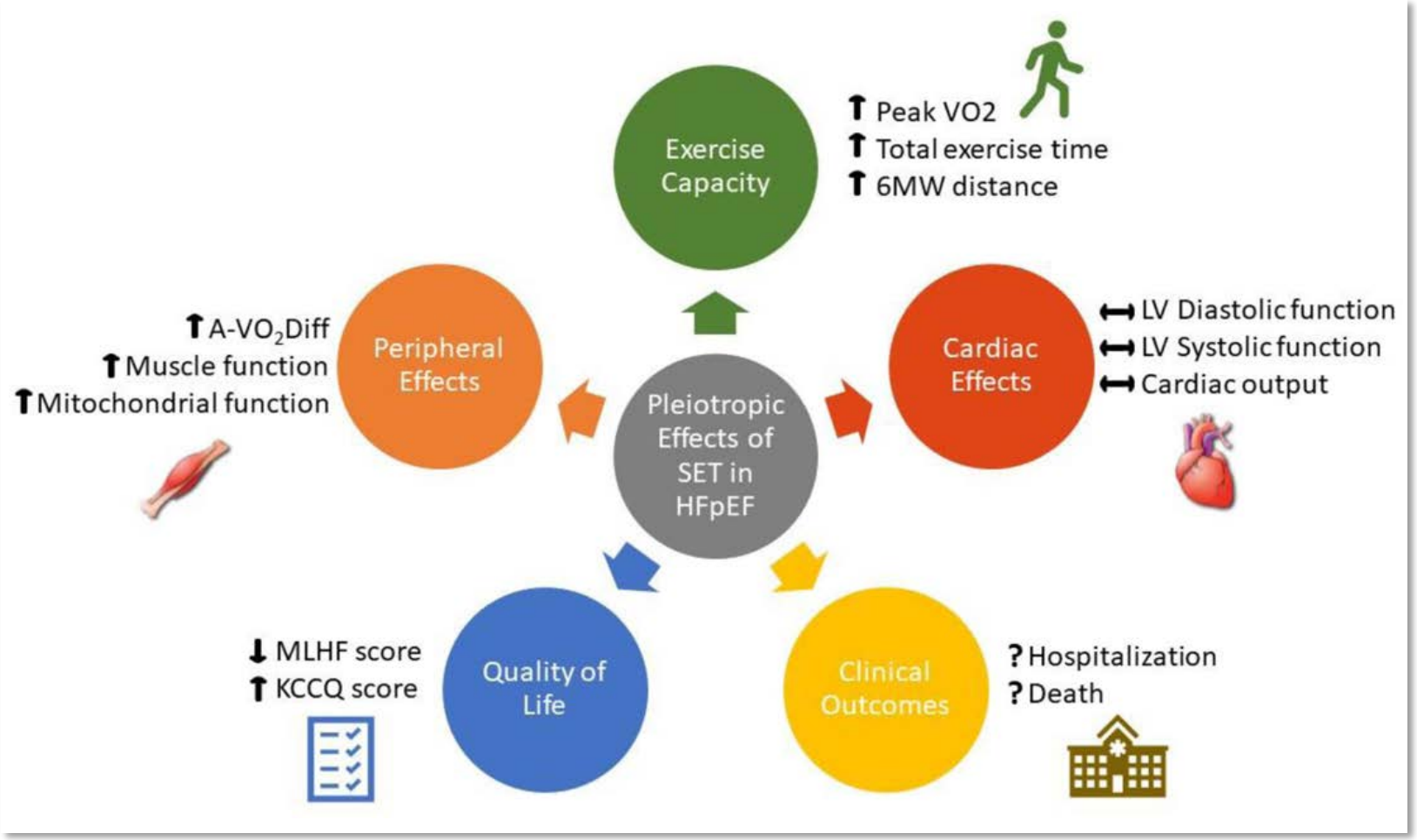






Supervised Exercise Training for Chronic Heart Failure With Preserved Ejection Fraction: A Scientific Statement From the American Heart Association and American College of Cardiology

- **El EF en IC-FEp, mejora la capacidad de ejercicio** (consumo de O2, Tiempo total de ejercicio), **la función de los musculos y mitocondrias así como la calidad de vida.**



Circulation. 2023;147:00–00. DOI: 10.1161/CIR.0000000000001122

Ensayos clínicos en ICFE preservada hasta 2019

DIG-PEF (1987)
Digoxina

PEP-CHF (2006)
Perindopril

VALIDD (2007)
Valsartan

RAAM-PEF (2011)
Eplerenona

ELANDD (2012)
Nebivolol
J-DHF (2012)
Carvedilol

1995-2000

2001-2005

2006-2009

2010-2015

2019

CHARM-p (2003)
Candesartan

I-PRESERVE (2008)
Irbesartan

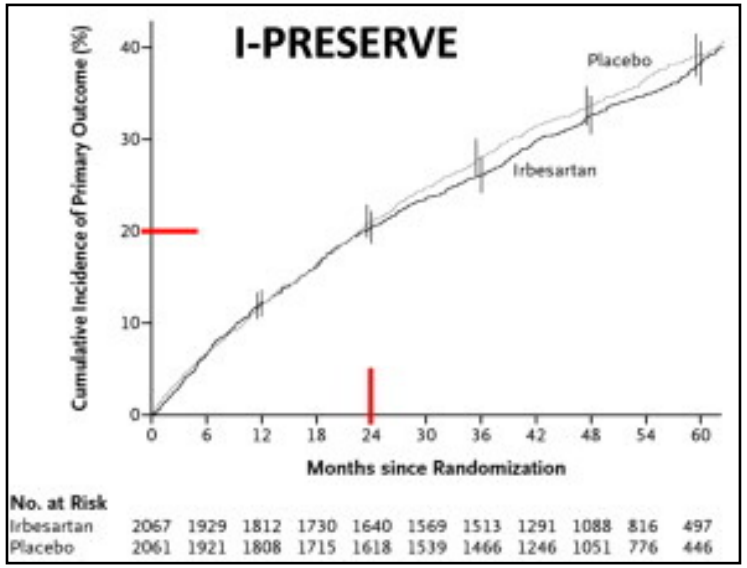
ALDO-DHF (2010)
Espironolactona

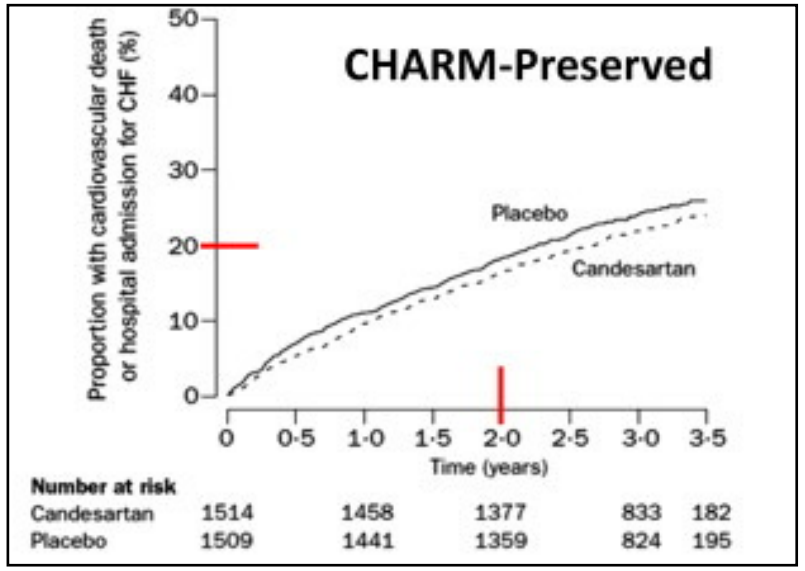
TOPCAT (2014)
Espironolactona

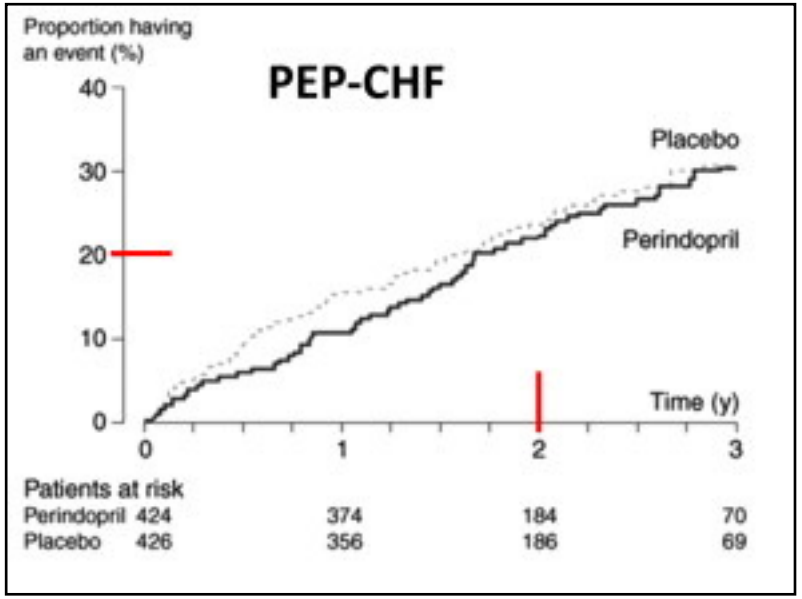
PARAGON-HF
(2019)
Sac/Val

RECORRIDO HISTÓRICO: IECA/ARA II

Study (publication year)	Drug or strategy	Number of patients	Main entry criteria	Primary end point	Finding	Notes	Refs
Angiotensin-converting enzyme inhibitor							
PEP-CHF (2006)	Perindopril	850	EF >40% plus SHD	All-cause death or HF hospitalization	Neutral	Improved 6-MWD, but high treatment discontinuation rates	26
Angiotensin receptor blocker							
CHARM-Preserved (2003)	Candesartan	3,023	EF >40%	CV-related death or HF hospitalization	Neutral	Greater benefit with lower EF, ↓ HF hospitalization	27
I-PRESERVE (2008)	Irbesartan	4,128	EF ≥45%	All-cause death or CV hospitalization	Neutral	Potential benefit in patients with low BNP levels	28







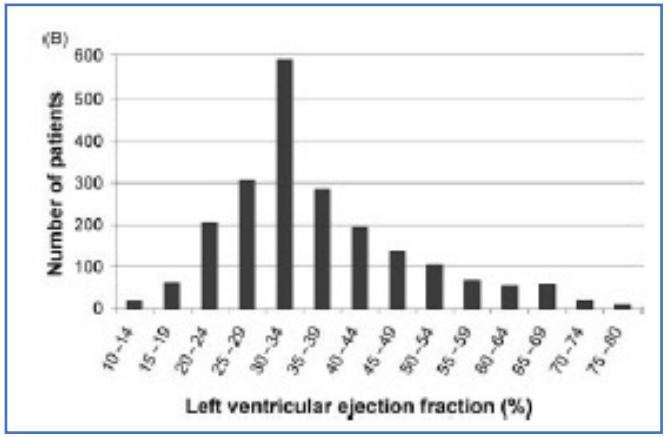
Borlaug, B.A. Nat Rev Cardiol 17, 559–573 (2020

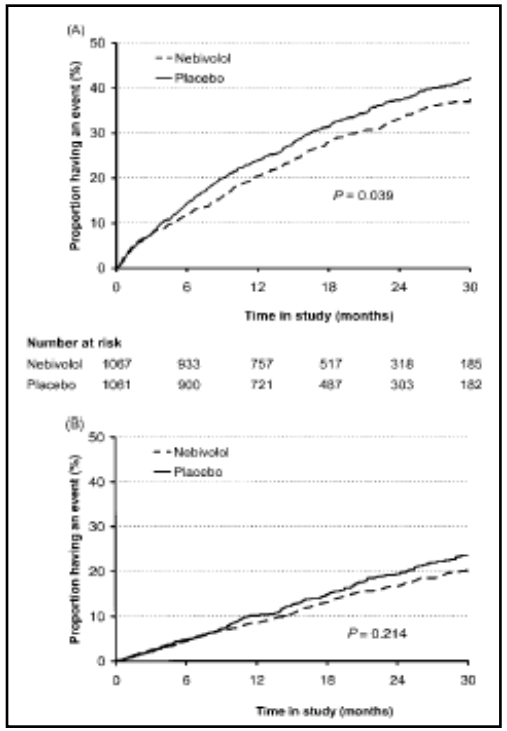
RECORRIDO HISTÓRICO: BB

Study (publication year)	Drug or strategy	Number of patients	Main entry criteria	Primary end point	Finding	Notes	Refs
β-Adrenergic receptor antagonist							
J-DHF (2013)	Carvedilol	245	EF >40%	CV-related death or HF hospitalization	Neutral	Open-label design, low event rate	
ELANDD (2012)	Nebivolol	116	EF >45% plus LVDD	6-MWD	Neutral	↓ HR correlated with ↓ exercise capacity	

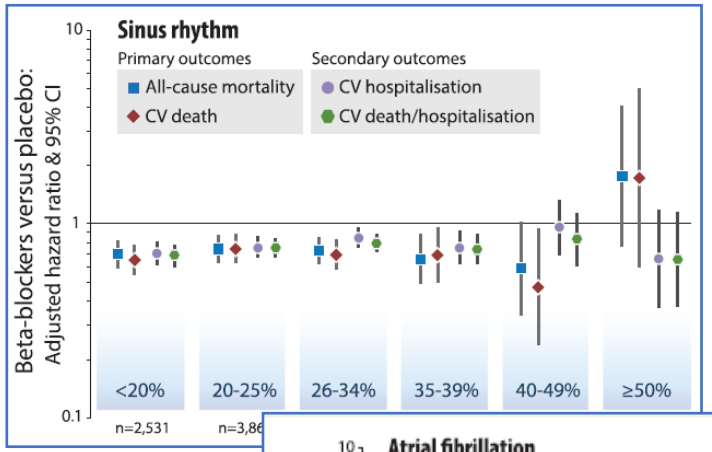
FASTTRACK Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)

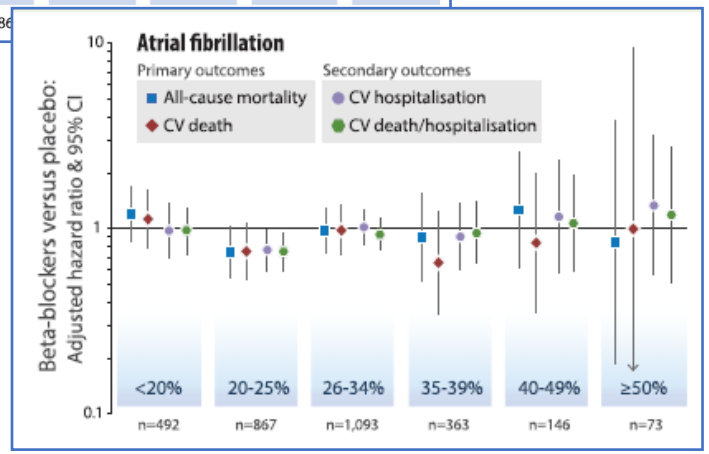
Solo un 15% de FEVI preservada





Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials





Borlaug, B.A. Nat Rev Cardiol 17, 559–573 (2020

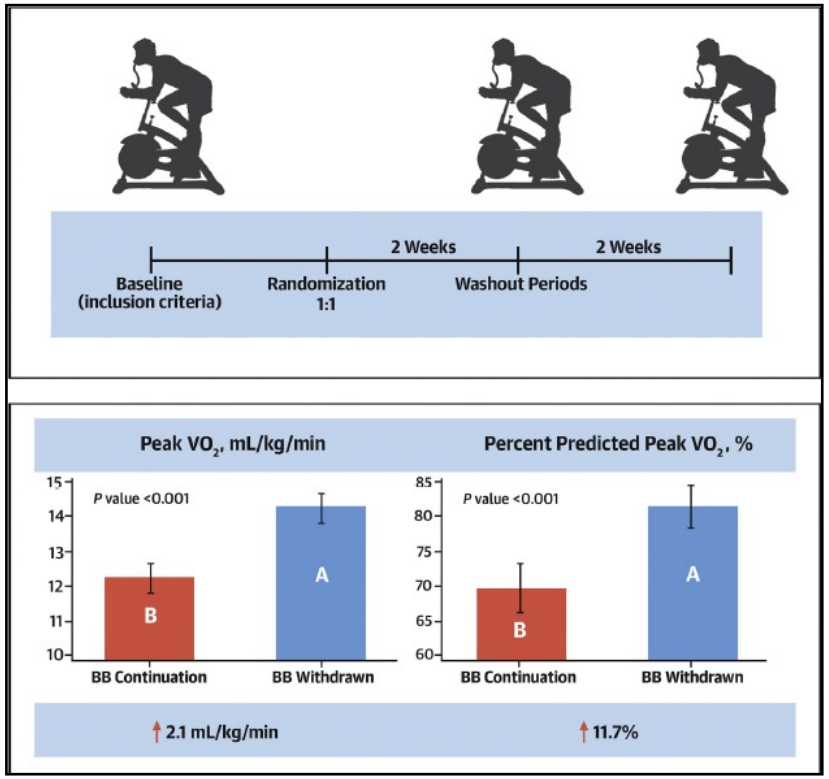
JACC 2009;53: 2150-8

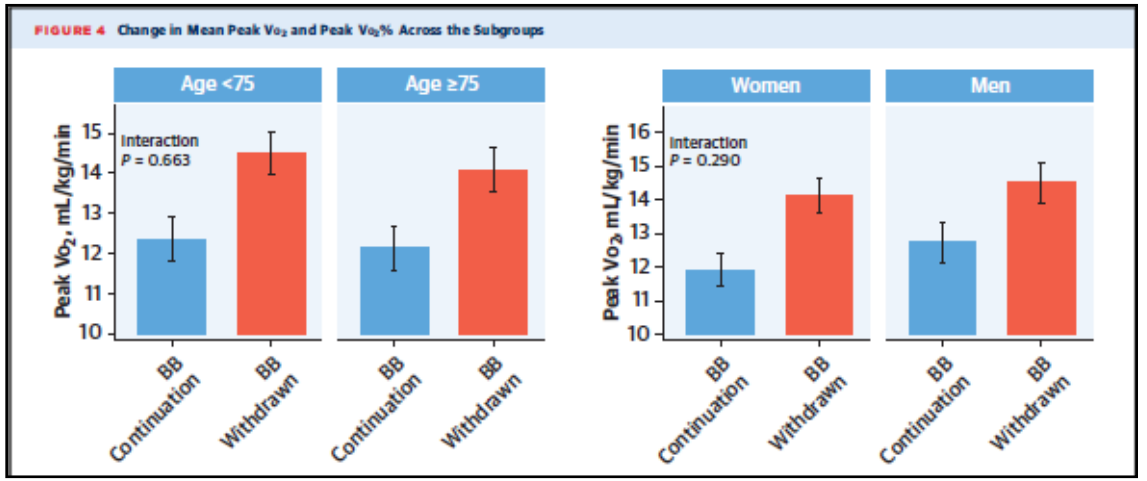
European Heart Journal (2018) 39, 26–35

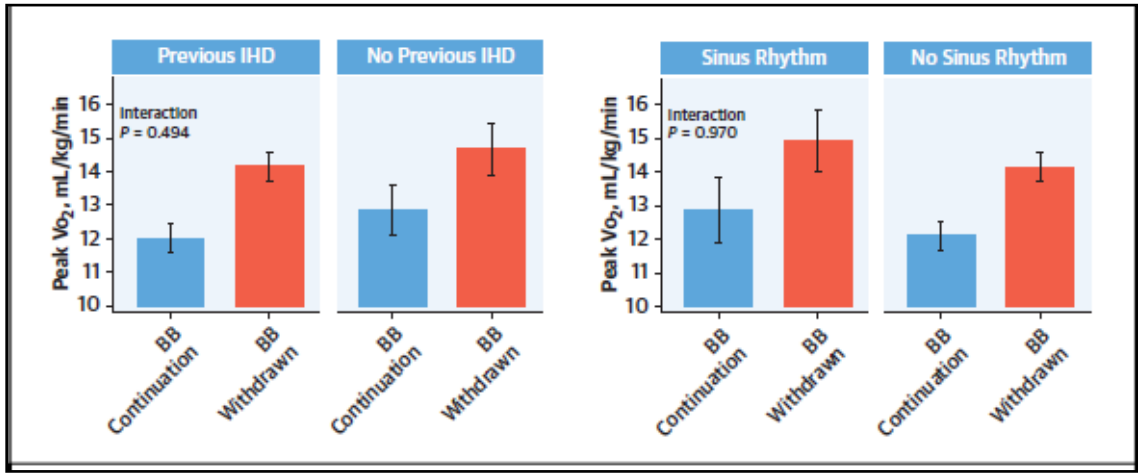
RECORRIDO HISTÓRICO: BB

Effect of β-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction

CON Insuficiencia cronotropa en ergometría







European Heart Journal (2018) 39, 26–35

RECORRIDO HISTÓRICO: ARM

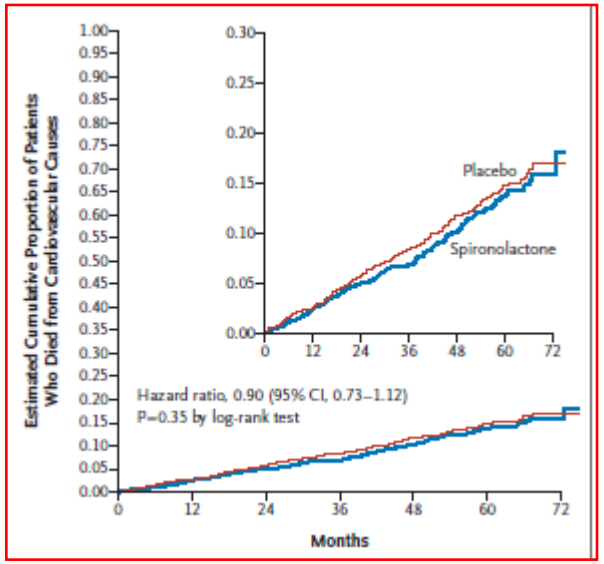
Study (publication year)	Drug or strategy	Number of patients	Main entry criteria	Primary end point	Finding	Notes	Refs
Mineralocorticoid receptor antagonist							
TOPCAT (2014)	Spironolactone	3,445	EF ≥45% and HF hospitalization or ↑ BNP levels	CV-related death, aborted SCD or HF hospitalization	Neutral	Geographical variation	82
Aldo-DHF (2013)	Spironolactone	422	EF ≥50% plus LVDD	Peak VO_2 and E/e'	Neutral	Favorable reduction in E/e', ↓ NT-proBNP levels, ↓ LV mass, no effect on QOL	83

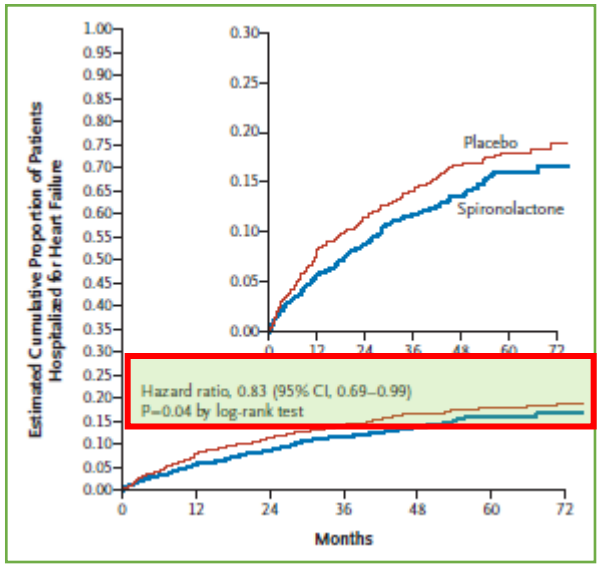
Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., and Sonja M. McKinlay, Ph.D., for the TOPCAT Investigators*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04

La espironolactona, como objetivo secundario,
↓ un 17% las hospitalizaciones por IC





Borlaug, B.A. Nat Rev Cardiol 17, 559–573 (2020

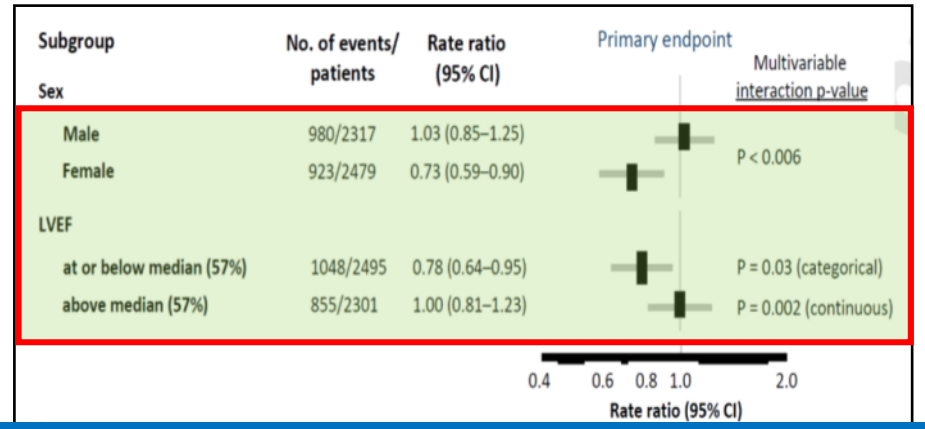
RECORRIDO HISTÓRICO: ARNi

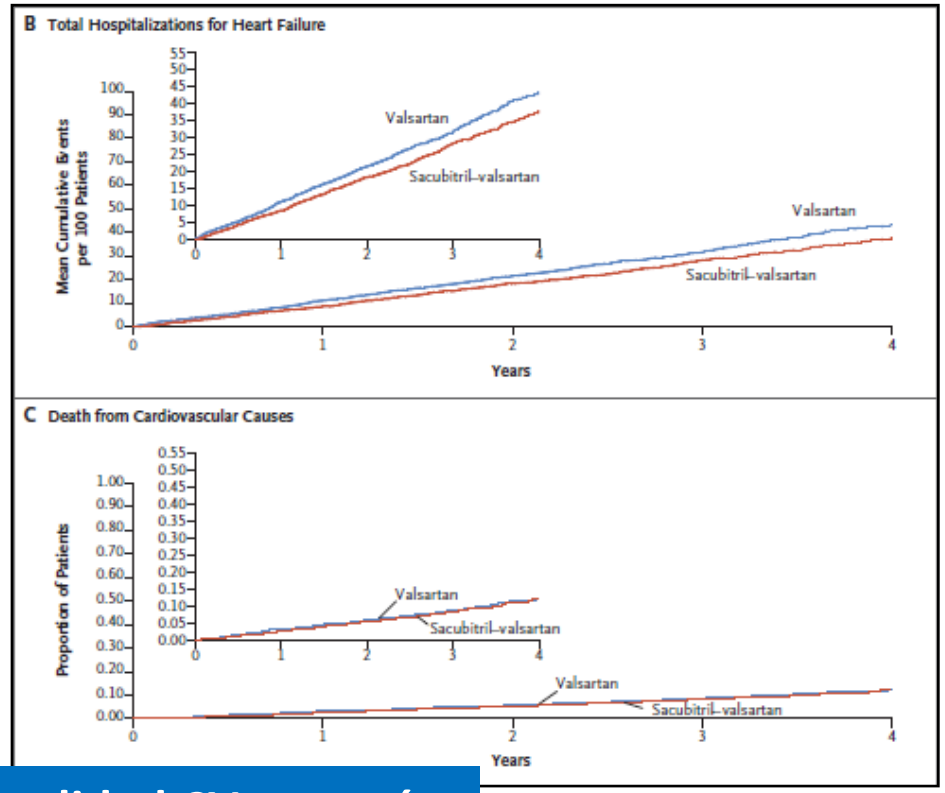
Study (publication year)	Drug or strategy	Number of patients	Main entry criteria	Primary end point	Finding	Notes	Refs
Angiotensin receptor–neprilysin inhibitor							
PARAMOUNT (2012)	Sacubitril–valsartan	301	EF ≥45%, ↑ BNP	Reduction in NT-proBNP levels	Positive	↓ LA volume	79
PARAGON (2019)	Sacubitril–valsartan	4,822	EF ≥45%, ↑ BNP plus SHD	CV-related death or HF hospitalization	Neutral	Possible benefit in women and patients with EF <57%	23

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)





ARNI como objetivo secundario ↓ la hospitalización por IC y la mortalidad CV en varón hasta 57% FEVi y en mujeres, también en FG<60 ml/min y tratados con ARM.

Borlaug, B.A. Nat Rev Cardiol 17, 559–573 (2020

Evolución del tratamiento de la IC con FEVIp

ESC 2016

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class[a]	Level[b]	Ref[c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

Diuréticos

Ponikowski P et al. Eur Heart Journal 2016

ESC 2021

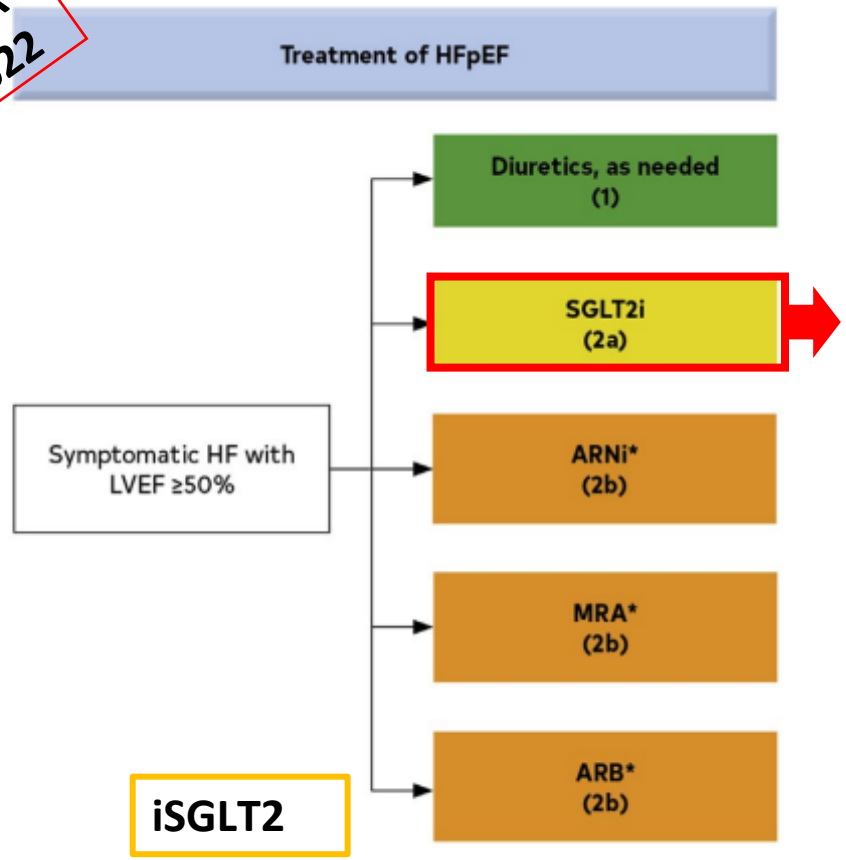
Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

Diuréticos

McDonagh T et al. Eur Heart Journal 2021

AHA 2022



iSGLT2

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.01

HASTA MEDIADOS DE 2021 ESTÁBAMOS… EN LA EDAD DE HIELO DE LA IC-FEp

La indicación para el tratamiento de la insuficiencia cardíaca crónica sintomática está pendiente de resolución de financiación y precio en el ámbito del Sistema Nacional de Salud.

Diapositiva creada por el autor

EL 6 de JULIO del 2021 VIMOS LA LUZ AL FINAL DEL TÚNEL DE LA IC-FEp

Breakthrough results for Jardiance® (empagliflozin) confirm EMPEROR-Preserved as first and only successful trial for heart failure with preserved ejection fraction

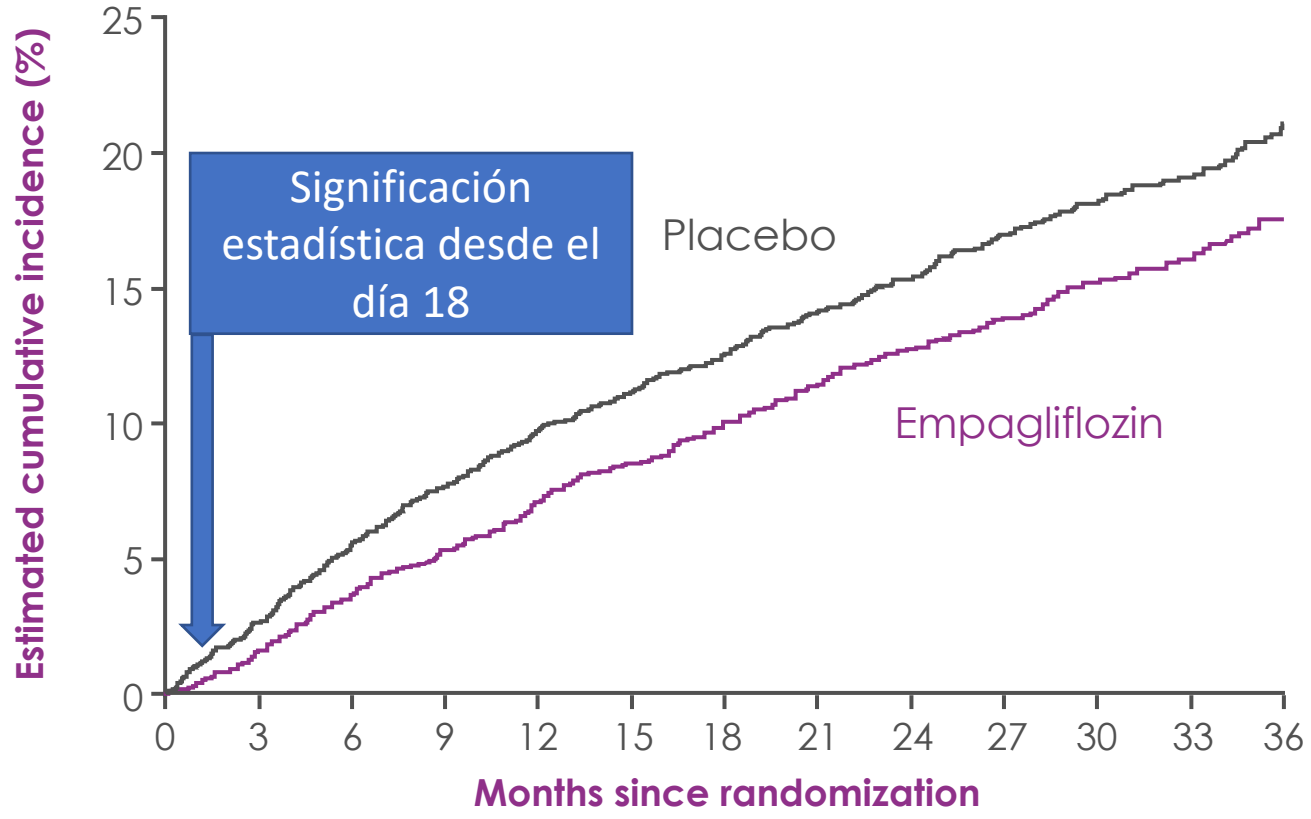
The EMPEROR-Preserved phase III trial met its primary endpoint, establishing Jardiance® (empagliflozin) as the first and only therapy to significantly reduce the risk of the composite of cardiovascular death or hospitalization for heart failure in adults, with or without diabetes, who live with heart failure with preserved ejection fraction (HFpEF). Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced the topline results today. When added to the EMPEROR-Reduced trial results, the(…) Read More »

emperor-preserved-heart-failure-full-data | Boehringer Ingelheim (boehringer-ingelheim.com)

La indicación para el tratamiento de la insuficiencia cardíaca crónica sintomática está pendiente de resolución de financiación y precio en el ámbito del Sistema Nacional de Salud.

Diapositiva creada por el autor

Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*=31

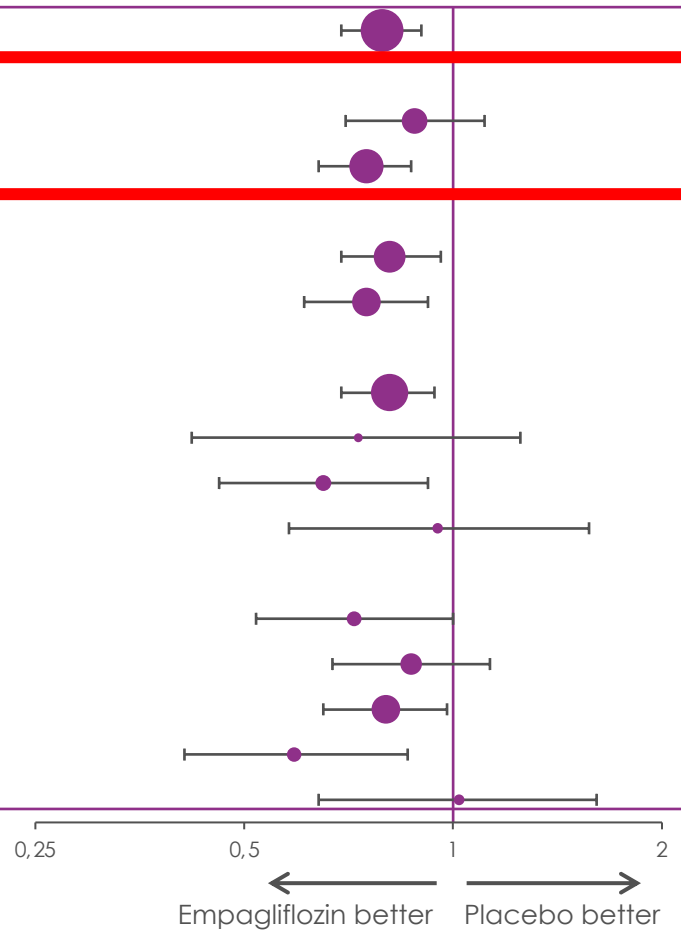
HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction. Anker S *et al. N Engl J Med*. 2021;XX:XXX.

EMPEROR-Preserved: Primary endpoint: Subgroup analysis

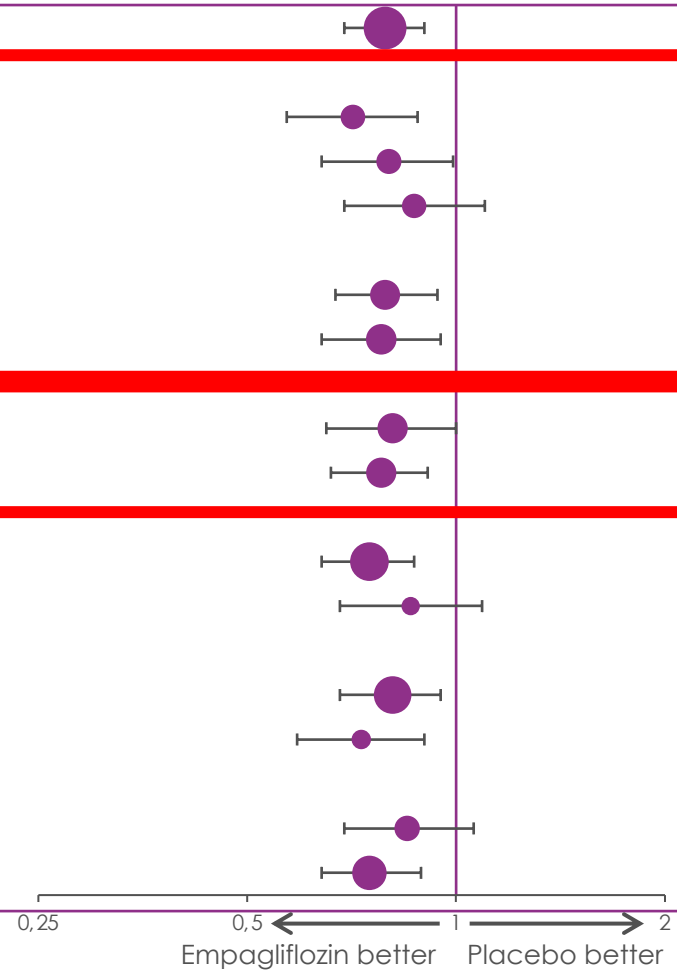
	Empagliflozin	Placebo	HR (95% CI)
	n with event/N analysed		
Overall	415/2997	511/2991	0.79 (0.69, 0.90)
Age, years			
<70	134/1066	152/1084	0.88 (0.70, 1.11)
≥70	281/1931	359/1907	0.75 (0.64, 0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69, 0.96)
Female	162/1338	214/1338	0.75 (0.61, 0.92)
Race			
White	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)
Region			
North America	64/360	83/359	0.72 (0.52, 1.00)
Latin America	105/758	120/757	0.87 (0.67, 1.13)
Europe	165/1346	202/1343	0.80 (0.65, 0.98)
Asia	45/343	69/343	0.59 (0.41, 0.86)
Other	36/190	37/189	1.02 (0.64, 1.61)



CI, confidence interval; HR, hazard ratio.
Anker S *et al. N Engl J Med*. 2021;XX:XXX.

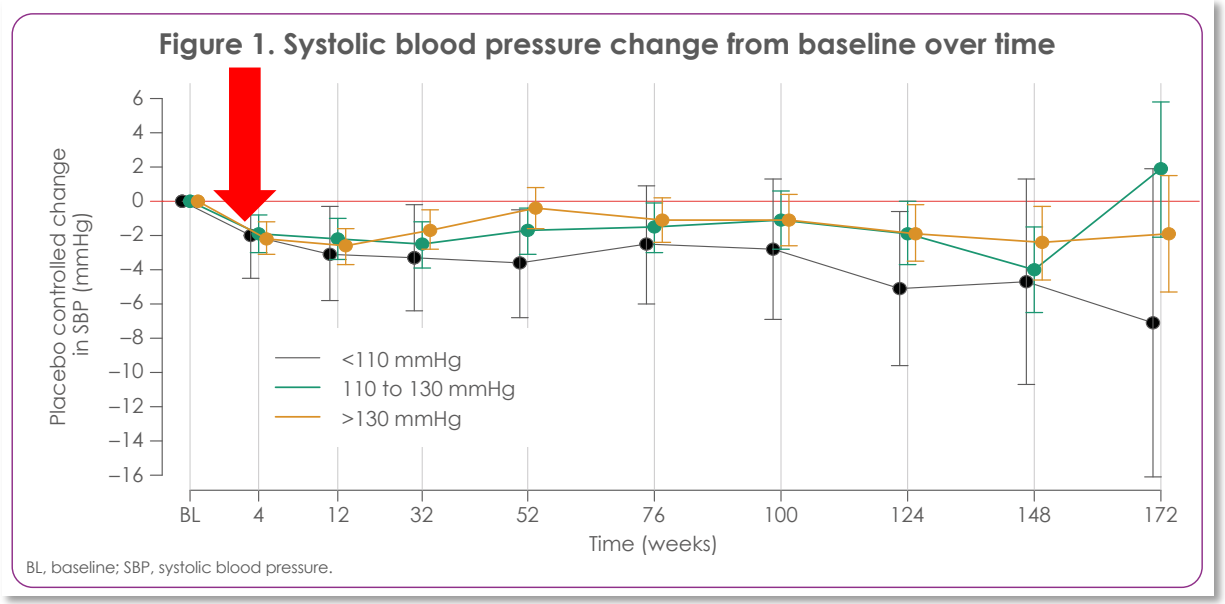
EMPEROR-Preserved: Primary endpoint: Subgroup analysis

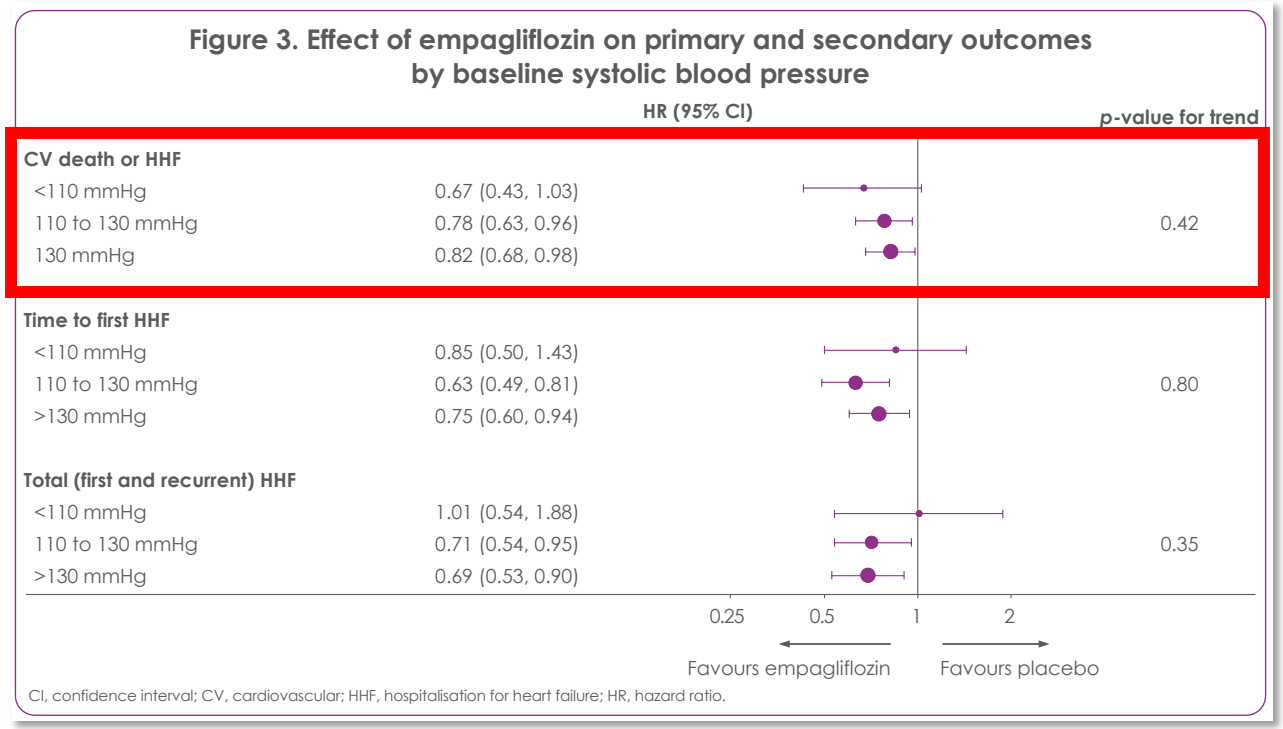
	Empagliflozin	Placebo	HR (95% CI)
	n with event/N analysed		
Overall	415/2997	511/2991	0.79 (0.69, 0.90)
Baseline LVEF			
<50%	145/995	193/988	0.71 (0.57, 0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64, 0.99)
≥60%	132/974	145/973	0.87 (0.69, 1.10)
Baseline diabetes status			
Diabetes	239/1466	291/1472	0.79 (0.67, 0.94)
No diabetes	176/1531	220/1519	0.78 (0.64, 0.95)
Baseline eGFR (CKD-EPI)			
≥60 mL/min/1.73 m²	152/1493	189/1505	0.81 (0.65, 1.00)
<60 mL/min/1.73 m²	263/1504	321/1484	0.78 (0.66, 0.91)
Baseline NYHA class			
II	275/2435	361/2452	0.75 (0.64, 0.87)
III/IV	140/562	150/539	0.86 (0.68, 1.09)
HF hospitalization in ≤12 months			
No	258/2298	319/2321	0.81 (0.68, 0.95)
Yes	157/699	192/670	0.73 (0.59, 0.90)
Cause of HF			
Ischaemic	157/1079	177/1038	0.85 (0.69, 1.06)
Non-ischaemic	258/1917	334/1953	0.75 (0.64, 0.89)



See slide notes for abbreviations. Anker S *et al. N Engl J Med*. 2021;XX:XXX.

Empagliflozin Improves Cardiovascular and Renal Outcomes in Patients with Preserved Ejection Fraction Irrespective of Blood Pressure: The EMPEROR-Preserved Trial





Poster 60572: Presented at the European Society of Cardiology – Heart Failure & World Congress on Acute Heart Failure 2022, Madrid, Spain, 21–24 May 2022. **Presenter:** Prof Michael Böhm, University Hospital of Saarland, Clinic for Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Homburg, Saarland, Germany; email: michael.boehm@uks.eu.

Empagliflozin Improves Cardiovascular and Renal Outcomes in Patients with Preserved Ejection Fraction Irrespective of Age: Insights from the EMPEROR-Preserved Trial

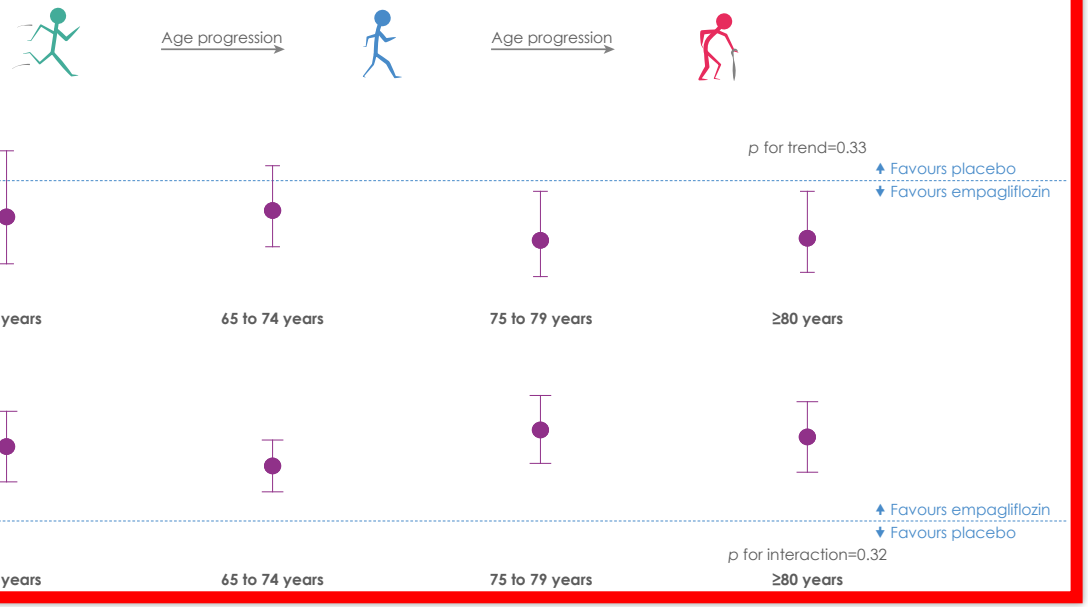
Table 1. Baseline characteristics by age groups

Characteristics	Age group				
	<65 years N=1199	65 to 74 years N=2214	75 to 79 years N=1276	≥80 years N=1299	*p*-value for trend
Sex, n (%)					
Male	760 (63.4)	1277 (57.7)	657 (51.5)	618 (47.6)	<0.0001
Female	439 (36.6)	937 (42.3)	619 (48.5)	681 (52.4)	

N>75 AÑOS = 2575

Mejorando la calidad de vida incluido en los pacientes >75 años

Figure 1. Treatment effect, empagliflozin versus placebo, for A. primary outcome (time-to-first CV death or HHF), B. eGFR slope and C. KCCQ-CSS-responder analysis at Week 52 by age



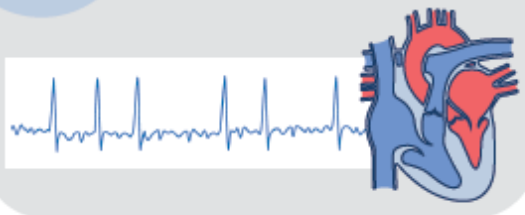
1.Poster 60570: Presented at the European Society of Cardiology – Heart Failure & World Congress on Acute Heart Failure 2022, Madrid, Spain, 21–24 May 2022.

Presenter: Prof Michael Böhm, University Hospital of Saarland, Clinic for Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Homburg, Saarland, Germany; email: michael.boehm@uks.eu.

Empagliflozin in heart failure with preserved ejection fraction with and without atrial fibrillation

KEY QUESTION: Does AF influence the treatment effect of empagliflozin on clinical outcomes in patients with HF with LVEF >40%?

52% of patients in the EMPEROR-Preserved trial had AF at baseline

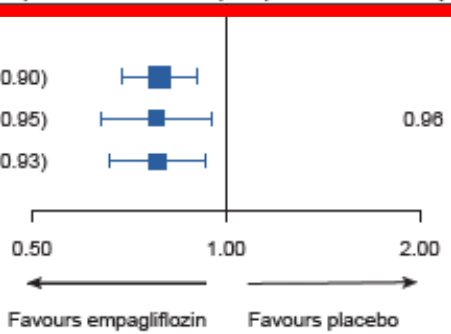


Baseline characteristics

AF (n=3135)		No AF (n=2844)
74 years	Mean age	70 years
20%	NYHA class III (%)	16%
25%	HHF <1 year ago	20%
1354	Median NT-proBNP (pg/mL)	614

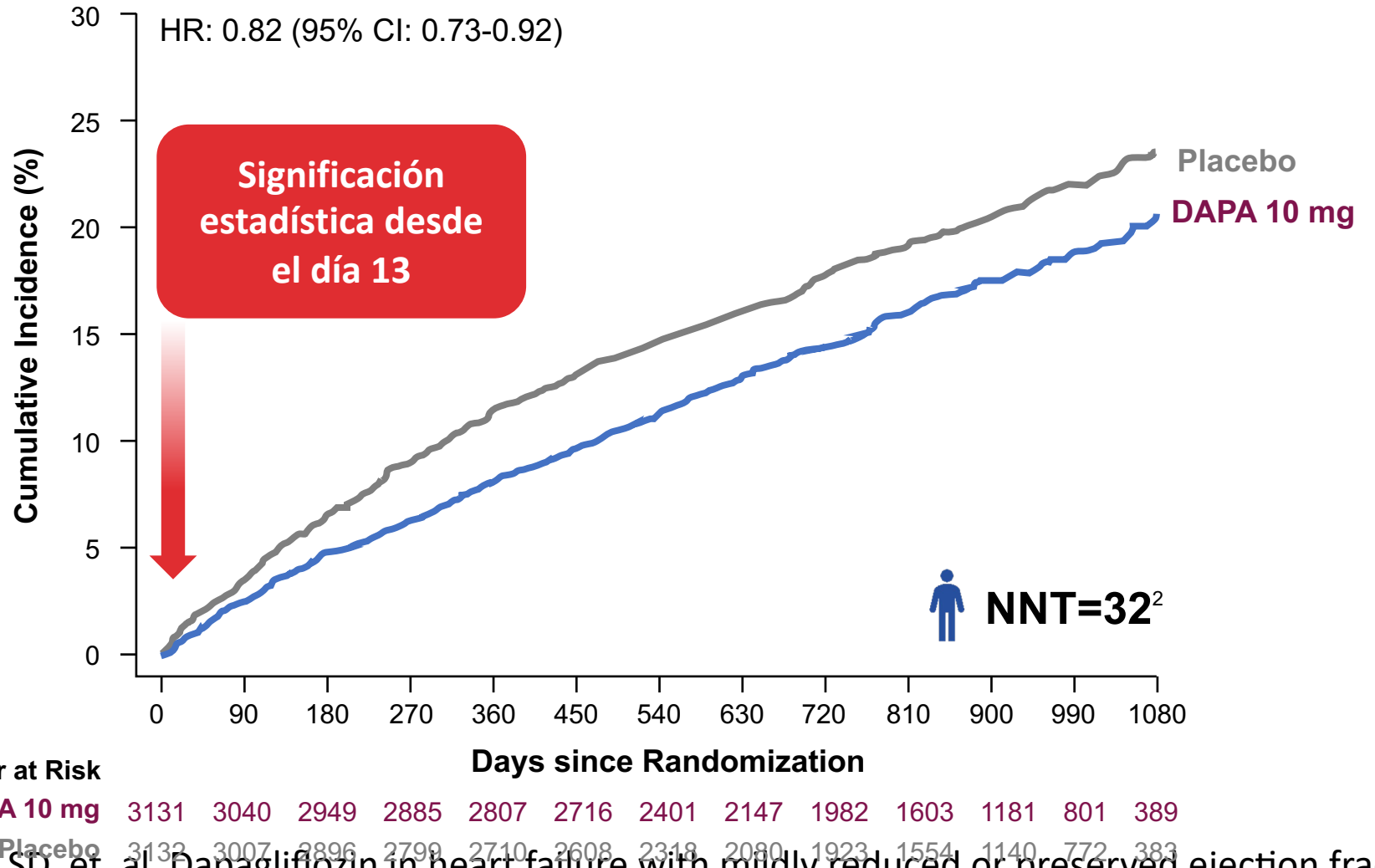
Empagliflozin reduced the risk of first HHF or CV death compared with placebo to a similar extent in patients with and without AF

	Empagliflozin 10 mg		Placebo				
	n/N (%)	Rate/100 py	n/N (%)	Rate/100 py	HR (95% CI)	HR (95%)	Interaction *p*-value
Primary outcome: Adjudicated first HHF or CV death							
All patients	415/2997 (13.8)	6.86	511/2991 (17.1)	8.67	0.79 (0.69, 0.90)		
No prevalent AF	170/1417 (12.0)	5.91	219/1427 (15.3)	7.74	0.78 (0.64, 0.95)		0.96
Prevalent AF	244/1576 (15.5)	7.72	292/1559 (18.7)	9.57	0.78 (0.66, 0.93)		



doi: 10.1002/ejhf.2861

Primary Composite of CV Death, hHF or Urgent HF Visit[1]



NEW!!

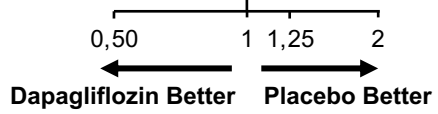
18 % RRR

3.1% ARR
p=0.0008[2]

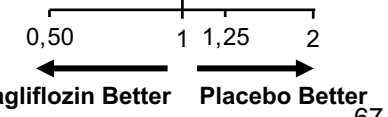
- 1. Solomon SD, et, al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa2206286 . 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

DELIVER CON BENEFICIO PREESPECIFICADO EN CADA SUBGRUPO

Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
Age, yr	≤72	247/1545	306/1604	0.82 (0.69-0.97)
	>72	265/1586	304/1528	0.81 (0.69-0.96)
Sex	Female	195/1364	243/1383	0.81 (0.67-0.97)
	Male	317/1767	367/1749	0.82 (0.71-0.96)
Race	Asian	97/630	106/644	0.91 (0.69-1.20)
	Black	21/81	19/78	1.08 (0.58-2.01)
	White	372/2214	461/2225	0.79 (0.69-0.90)
	Other	22/206	24/185	0.83 (0.46-1.48)
Region	Europe/ Saudi Arabia	261/1494	309/1511	0.83 (0.70-0.98)
	Asia	92/607	103/619	0.89 (0.67-1.18)
	Latin America	70/602	87/579	0.78 (0.57-1.07)
	North America	89/428	111/423	0.75 (0.57-1.00)
T2D	Yes	270/1401	317/1405	0.83 (0.70-0.97)
	No	242/1730	293/1727	0.81 (0.68-0.96)
AF/AFL on ECG	Yes	227/1327	271/1317	0.81 (0.68-0.97)
	No	285/1803	339/1814	0.82 (0.70-0.96)
BMI, kg/m²	<30	275/1734	302/1736	0.89 (0.75-1.04)
	≥30	236/1395	308/1392	0.74 (0.63-0.88)

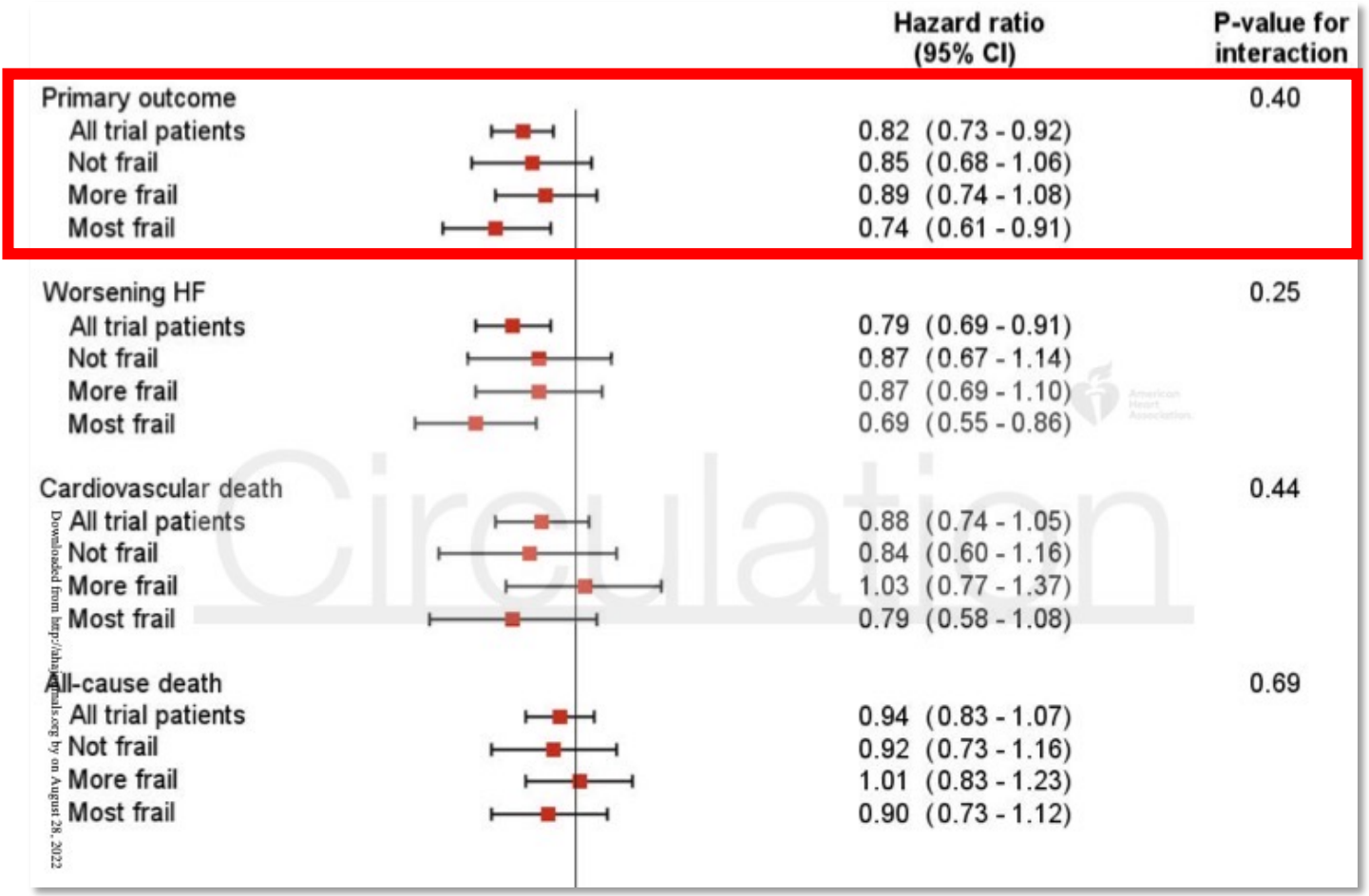


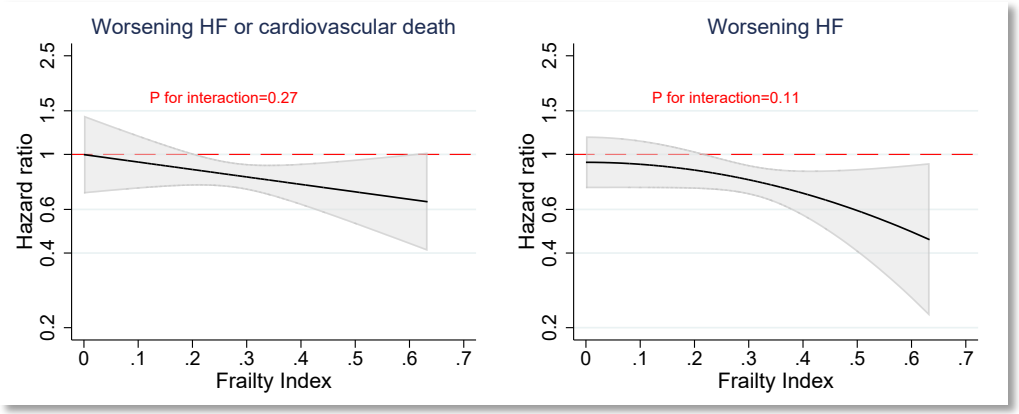
Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
NYHA class	II	331/2314	411/2399	0.81 (0.70-0.94)
	III or IV	181/817	198/732	0.80 (0.65-0.98)
LVEF, %	≤49	207/1067	229/1049	0.87 (0.72-1.04)
	50-59	174/1133	211/1123	0.79 (0.65-0.97)
	≥60	131/931	170/960	0.78 (0.62-0.98)
NT-proBNP, pg/mL	≤1011	173/1555	208/1578	0.84 (0.68-1.02)
	>1011	339/1576	402/1553	0.79 (0.69-0.92)
Enrollment during or within 30 days of hHF	Yes	93/328	113/326	0.78 (0.60-1.03)
	No	419/2803	497/2806	0.82 (0.72-0.94)
Prior LVEF ≤40%	Yes	92/572	119/579	0.74 (0.56-0.97)
	No	420/2559	491/2553	0.84 (0.73-0.95)
eGFR, mL/min/1.73 m²	<60	289/1516	355/1554	0.81 (0.69-0.94)
	≥60	223/1615	255/1577	0.84 (0.70-1.00)
SBP, mmHg	≤128	280/1568	300/1590	0.93 (0.79-1.10)
	>128	232/1563	310/1542	0.71 (0.60-0.85)



- Solomon SD, et, al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa2206286

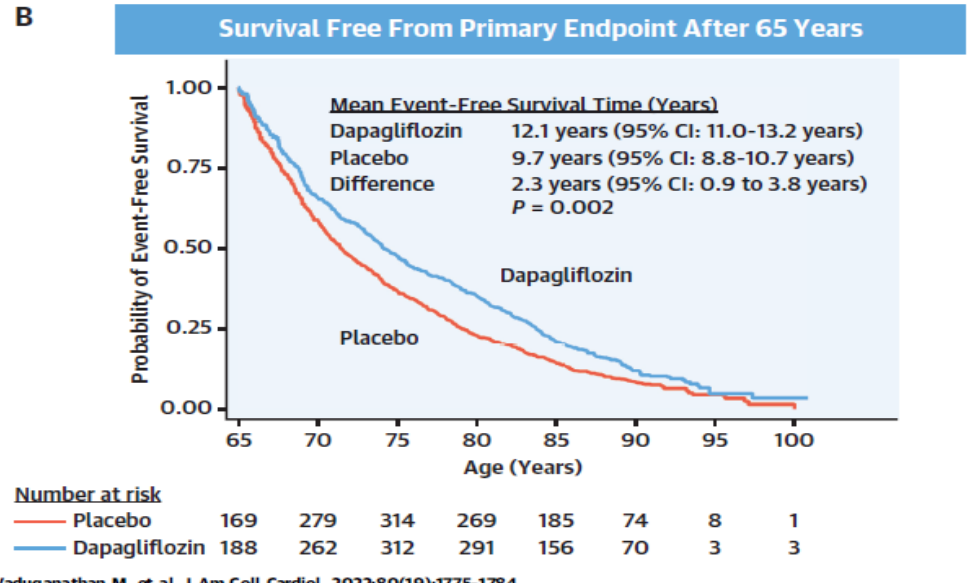
Efficacy and Safety of Dapagliflozin According to Frailty in Patients with Heart Failure: A Prespecified Analysis of the DELIVER Trial

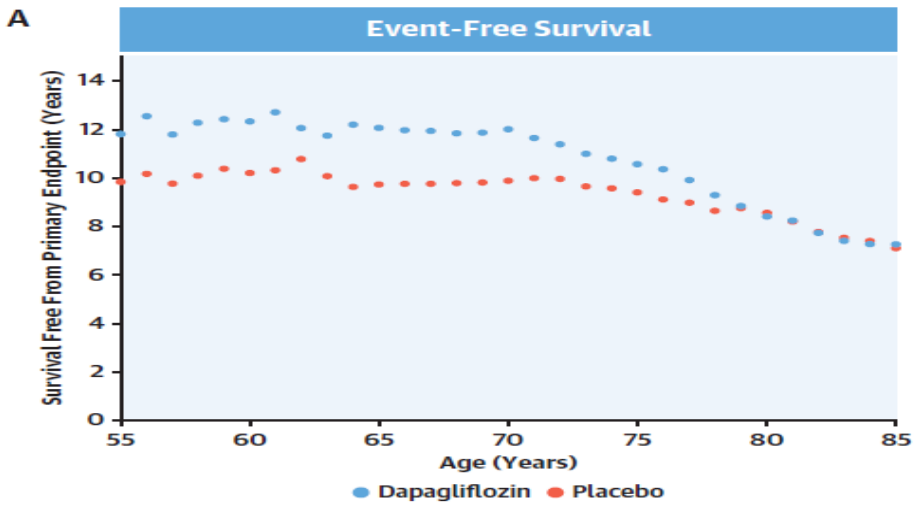


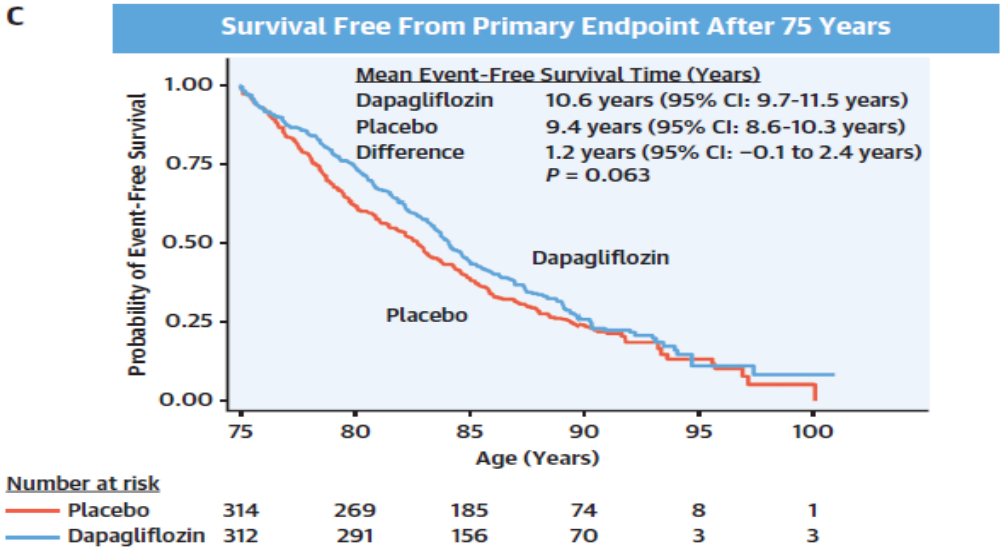


10.1161/CIRCULATIONAHA.122.061754

Beneficio estimado con Dapagliflocina a largo plazo en pacientes con ICFEp- DELIVER





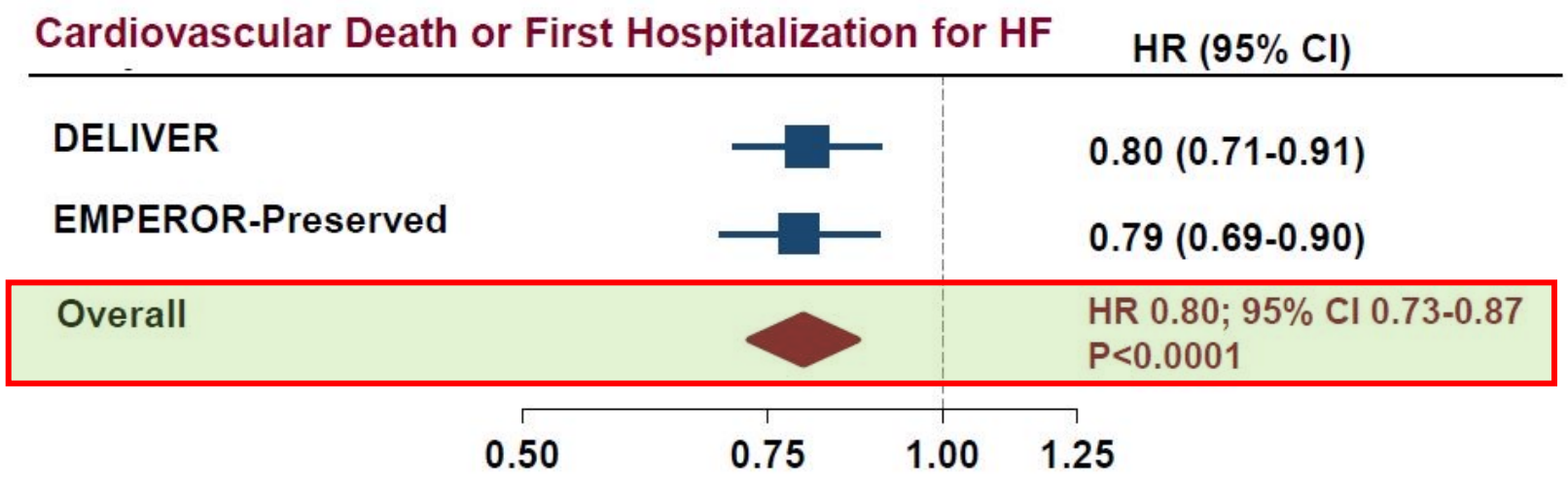


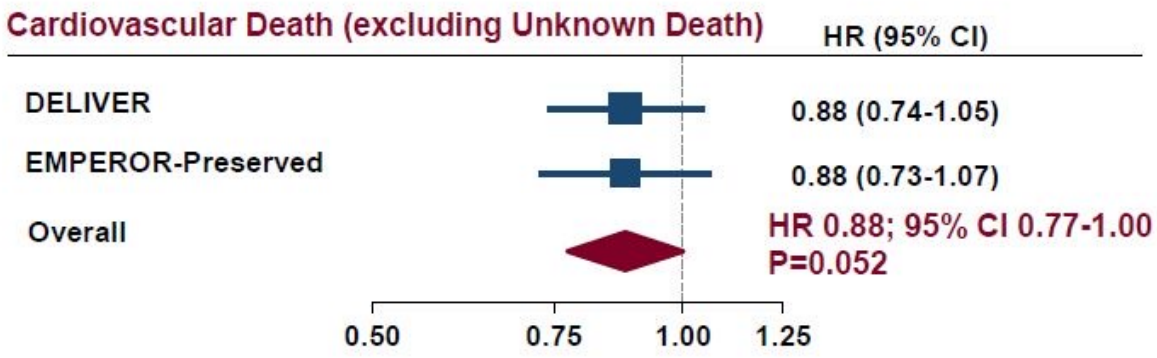
- Supervivencia libre de eventos con Dapagliflocina aumenta frente a placebo en **2-2,5 años** en individuos de mediana edad y ancianos con ICFEp
- Efecto atenuado a partir de los 80 años

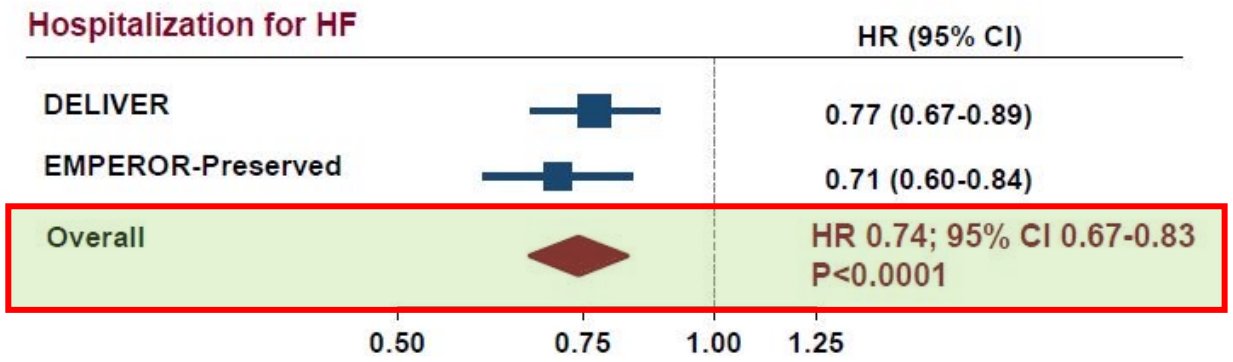
Vaduganathan M, et al. J Am Coll Cardiol. 2022;80(19):1775-1784.

Vaduganathan M et al. JACC 2022

iSGLT2 en pacientes con IC y FE preservada





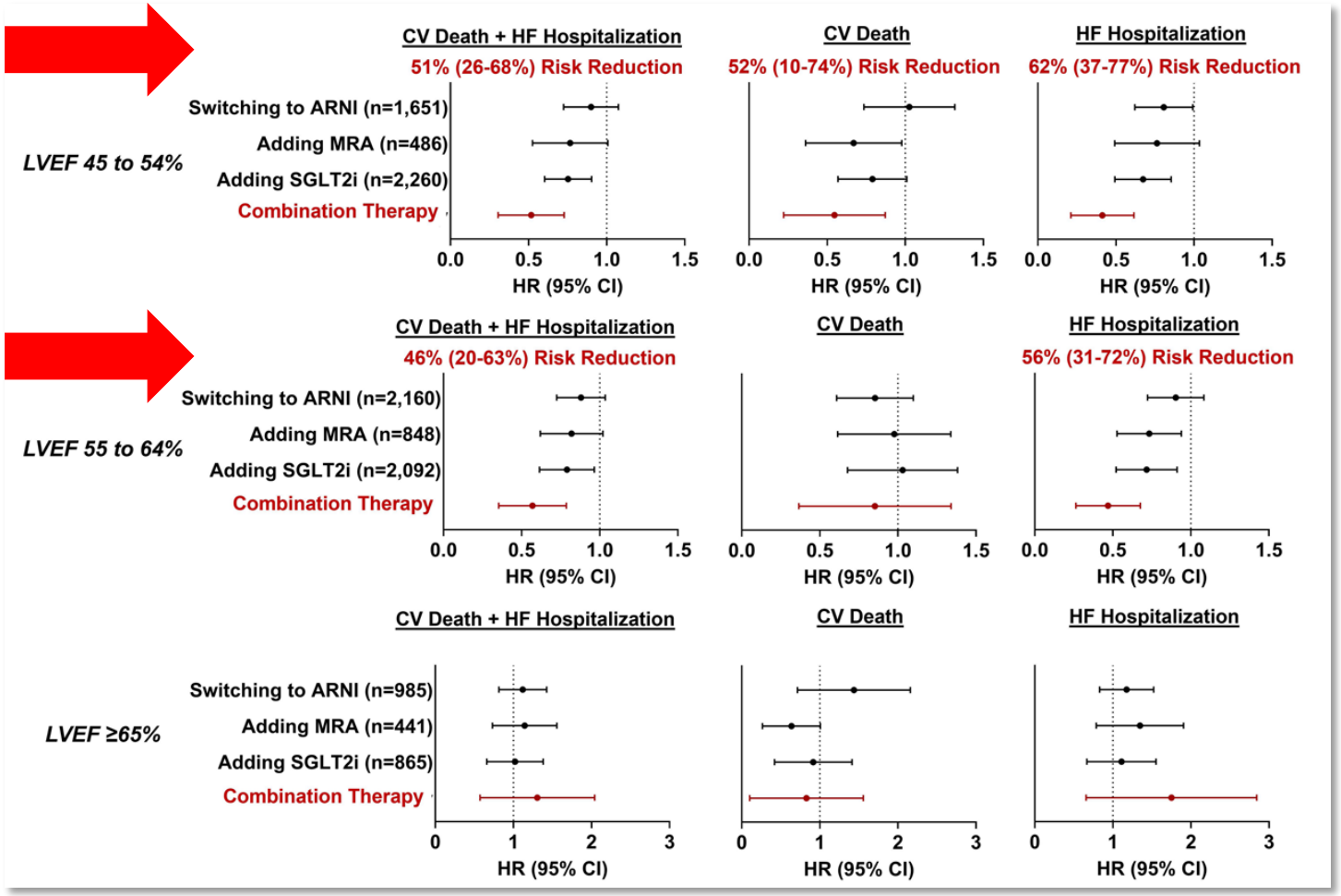


Vaduganthan M Lancet 2022; doi: 10.1016/S0140-6736(22)02074-8

RESEARCH LETTER

Estimating the Benefits of Combination Medical Therapy in Heart Failure With Mildly Reduced and Preserved Ejection Fraction

Muthiah Vaduganathan, MD; Brian L. Claggett, PhD; Riccardo M. Inciardi, MD; Gregg C. Fonarow, MD; John J.V. McMurray, MD; Scott D. Solomon, MD



LOS BENEFICIOS DE LA TRIPLE TERAPIA CON ARM+ARNI+iSGLT2 SE PRODUCE ENTRE 40-65%:

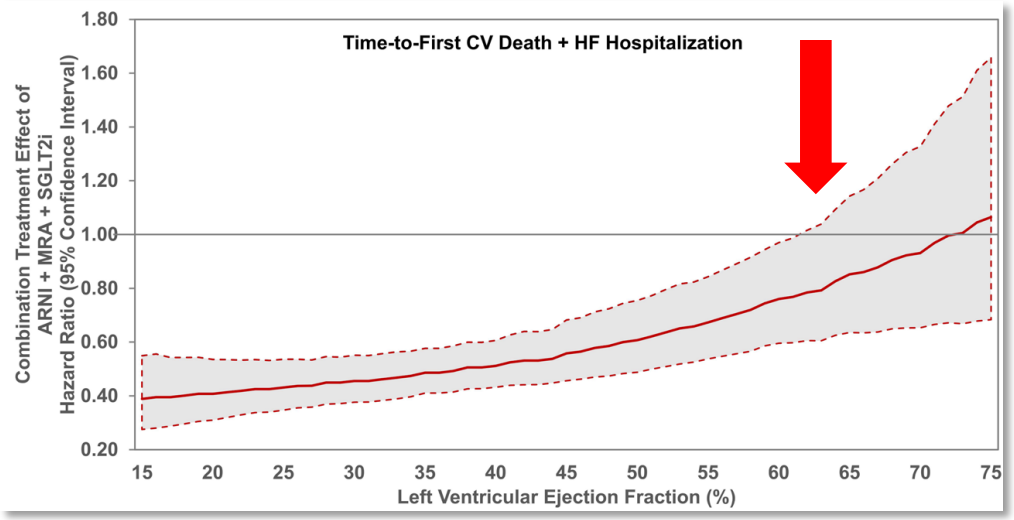
A. ***FEVi: 45-54% Reduce un 51% el RR de mortalidad CV e ingresos por IC.***

B. ***FEVi: 55-64% Reduce un 46% el RR de mortalidad CV e ingresos por IC.***

TOPCAT Funded by the NHLBI

PARAGONHF

EMPEROR PRESERVED



Circulation. 2022;145:00–00. DOI: 10.1161/CIRCULATIONAHA.121.058929

ESC European Society of Cardiology

European Journal of Heart Failure (2023)
doi:10.1002/ejhf.2864

RESEARCH ARTICLE

Potential global impact of sodium–glucose cotransporter-2 inhibitors in heart failure

Global HF Prevalence

64 million

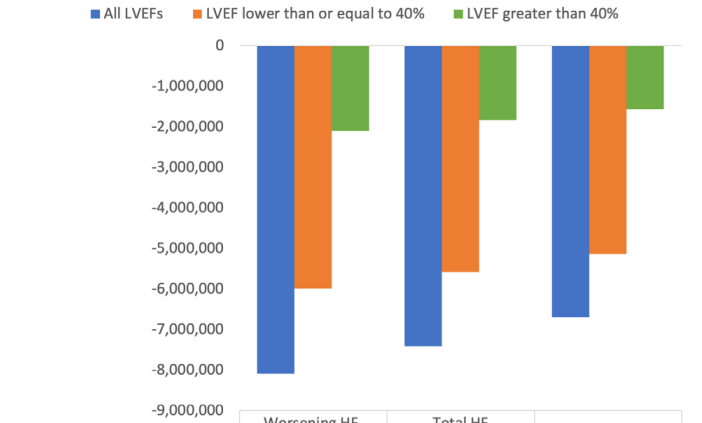
Estimated HF patients eligible for **SGLT-2 inhibitors** → **50 million**

Number needed to treat to prevent one **worsening HF event** or **cardiovascular death** with SGLT-2 inhibitors over 3 years → **LVEF ≤40%: 5 – 6**; **LVEF >40%: 10 – 12**

Projected global reduction in **worsening HF events** and **cardiovascular deaths** with optimal implementation over 3 years → **7 – 8 million**

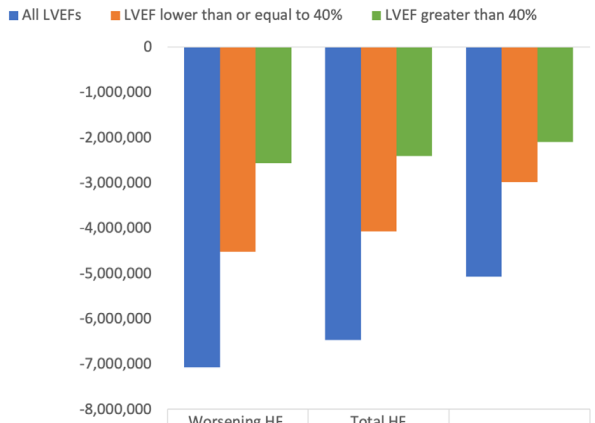
HF: heart failure; LVEF: left ventricular ejection fraction; SGLT-2: sodium-glucose cotransporter-2

EMPEROR-Reduced and EMPEROR-Preserved



	Worsening HF events and CV deaths	Total HF hospitalizations and CV deaths	Total HF hospitalizations
All LVEFs	-8,089,549	-7,411,770	-6,695,513
LVEF lower than or equal to 40%	-5,986,943	-5,579,093	-5,132,765
LVEF greater than 40%	-2,102,606	-1,832,677	-1,562,748

DAPA-HF and DELIVER



	Worsening HF events and CV deaths	Total HF hospitalizations and CV deaths	Total HF hospitalizations
All LVEFs	-7,069,235	-6,469,198	-5,066,481
LVEF lower than or equal to 40%	-4,512,011	-4,068,249	-2,978,081
LVEF greater than 40%	-2,557,224	-2,400,949	-2,088,400

European Journal of Heart Failure (2023) doi:10.1002/ejhf.2864

Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF

Brief Title: Pooled Analysis of PARAGLIDE-HF and PARAGON-HF

Key Question

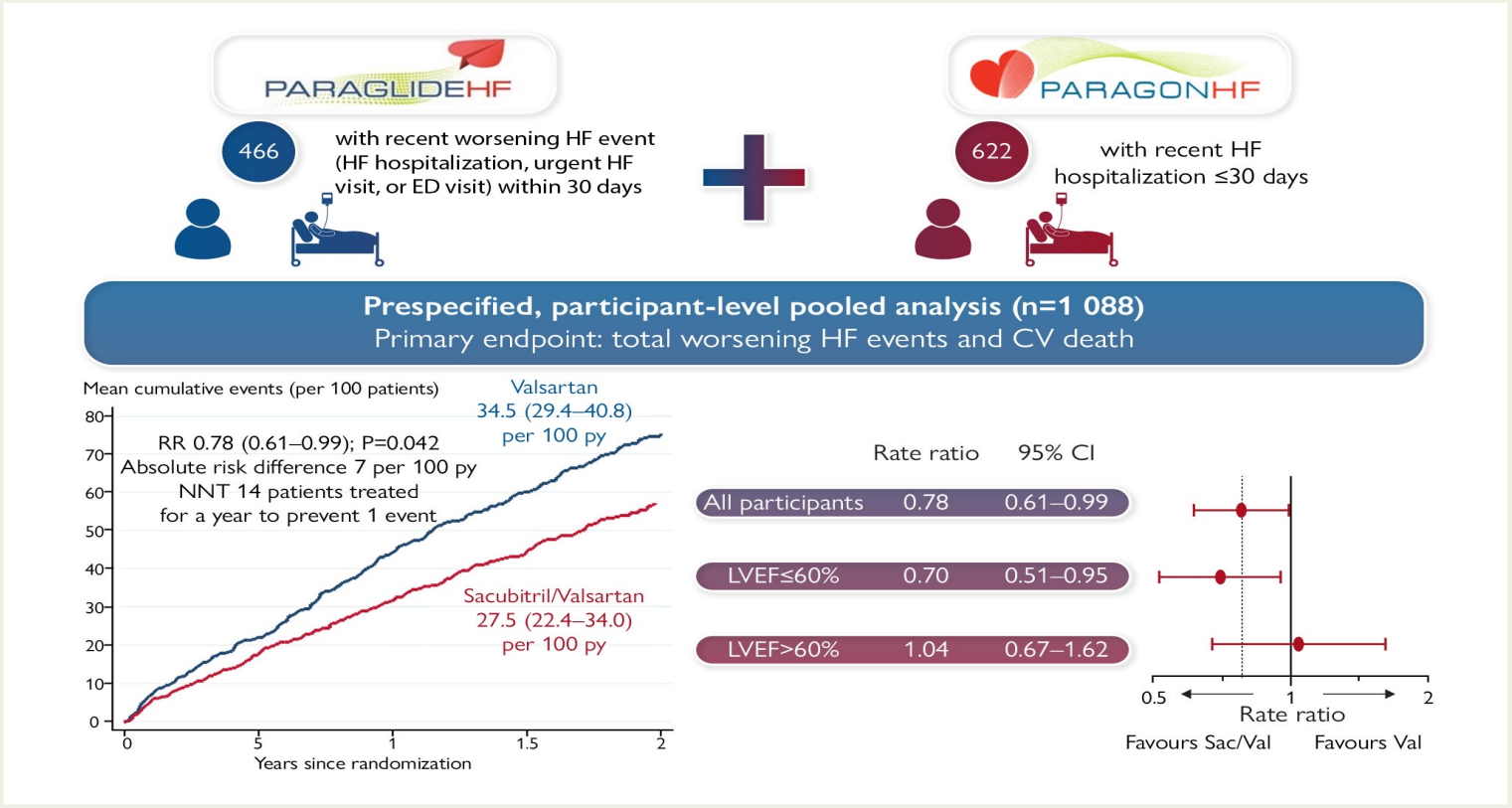
What is the efficacy and safety of sacubitril/valsartan compared with valsartan on cardiovascular and renal outcomes in patients with heart failure (HF) with mildly reduced or preserved ejection fraction?

Key Finding

In a prespecified, participant-level pooled analysis of PARAGLIDE-HF and the PARAGON-HF subset that was recently hospitalized for HF, sacubitril/valsartan significantly reduced total worsening HF events and cardiovascular death (rate ratio 0.78; 95% confidence interval 0.61-0.99; P=0.042). Treatment benefits tended to be larger in those with left ventricular ejection fraction (LVEF)≤60%.

Take Home Message

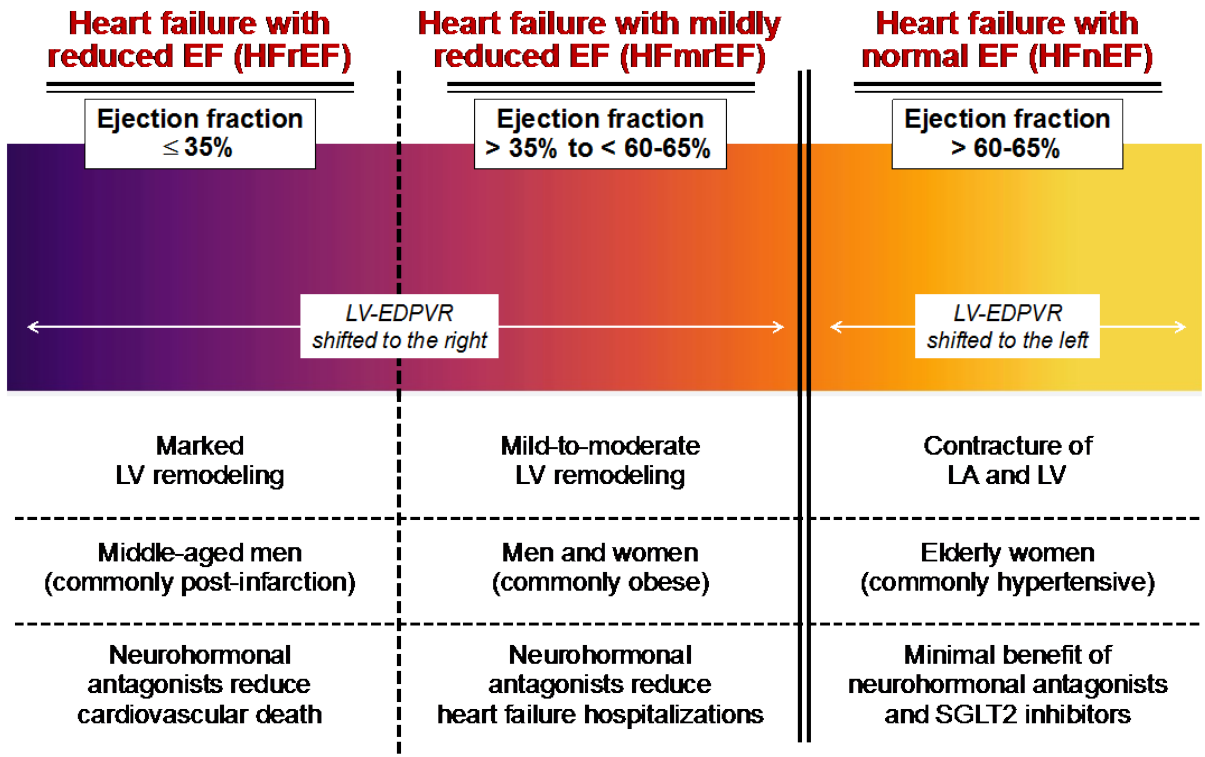
These data strengthen the current evidence base supporting the use of sacubitril/valsartan in patients with heart failure with mildly reduced or preserved ejection fraction, particularly among those with an LVEF below normal, regardless of care setting.



Eur Heart J, ehad344, https://doi.org/10.1093/eurheartj/ehad344

A Reclassification of Heart Failure Based on Recognition of Heart Failure With Normal to Supranormal Ejection Fraction, a Clinically Common Form of Cardiac Contracture, With Distinctive Pathophysiological and Therapeutic Features

Figure 1.
Reclassification of Heart Failure Based on Left Ventricular Remodeling and Contracture Phenotypes



doi: 10.1002/ejhf.2849

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

Treatment of heart failure with preserved ejection fraction (HFpEF)

STRONGLY RECOMMENDED

- **Sodium-glucose cotransporter type 2 inhibitor**
  Unless type 1 diabetes, history of diabetic ketoacidosis, or estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2
- **HF self-care plan education**
  Includes adherence to medications and sodium, calorie, and fluid restrictions, along with monitoring of weight, vital signs, and HF symptoms
- **Aerobic exercise training**
- **Diet-induced weight loss plus aerobic exercise for patients with obesity**
- **Loop diuretics for patients with fluid overload**
- **Manage hypertension (HTN) according to HTN guidelines**

CAN BE BENEFICIAL

- **Manage atrial fibrillation (AF) according to AF guidelines**

MAY BE CONSIDERED

- **Mineralocorticoid receptor antagonist such as spironolactone if:**
  EF <60%, elevated brain natriuretic peptide (BNP) assay, recent HF hospitalization, eGFR >30 mL/min/1.73 m^2 or creatinine <2.5 mg/dL, serum potassium <5.0 mmol/L, and adherent to laboratory monitoring
- **Angiotensin receptor-neprilysin inhibitor such as sacubitril valsartan if:**
  EF <45% for men or <60% for women and there are risk factors for HF hospitalization (elevated BNP assay, structural heart disease, or recent HF hospitalization)
- **Angiotensin receptor blocker such as candesartan if EF <55%**
- **Pulmonary artery pressure-guided therapy to reduce HF hospitalizations if:**
  NYHA class II-III symptoms of HF and elevated BNP/NT-proBNP or recent HF hospitalization

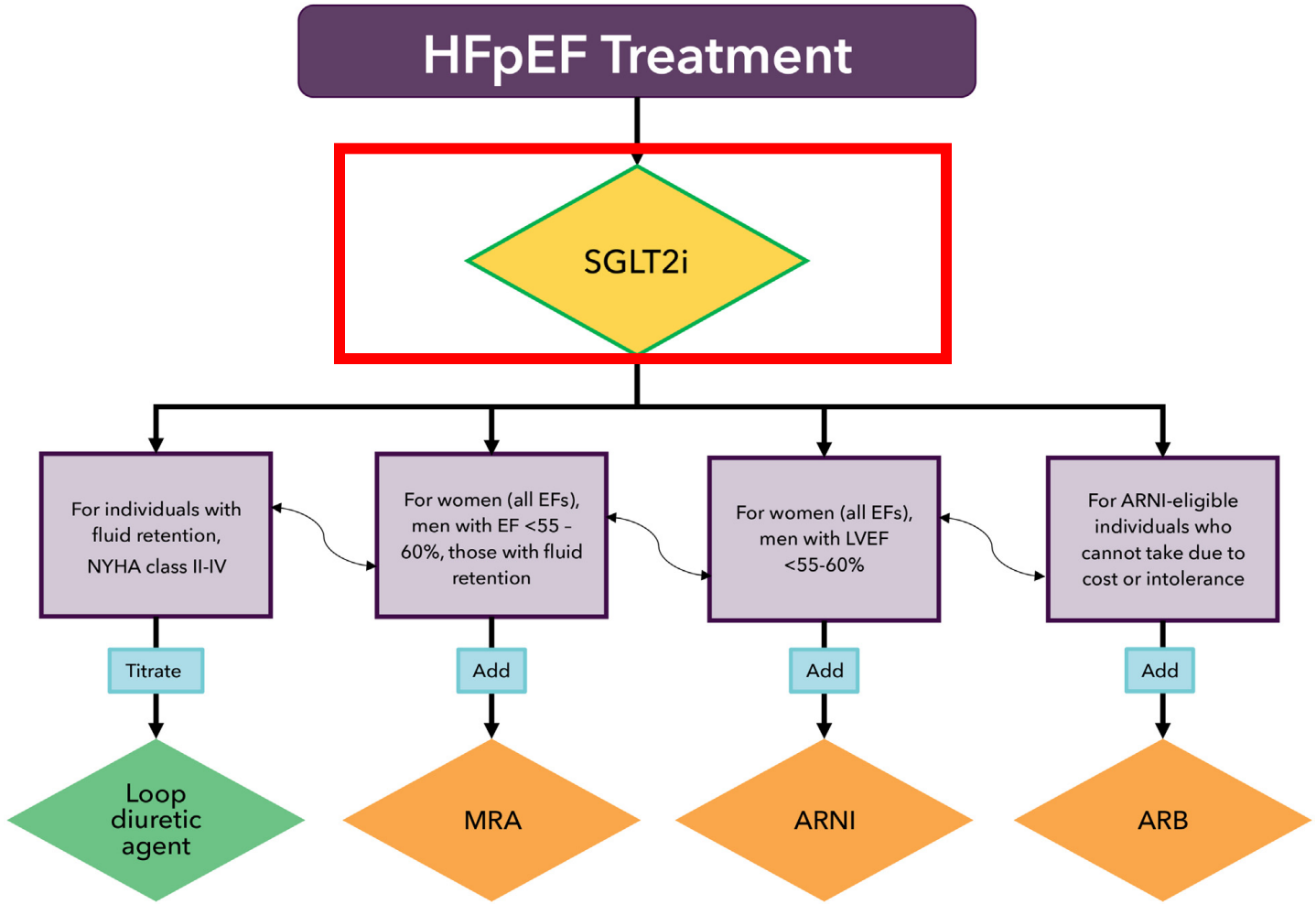
POTENTIALLY HARMFUL OR NONBENEFICIAL

(No benefit on exercise capacity or quality of life)

- **Nitrates, sildenafil, and soluble guanylate cyclase stimulators in patients with HFpEF**
- **Rate-adaptive atrial pacing in patients with HFpEF and chronotropic incompetence**

JAMA. 329(10):827-838, March 14, 2023.

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.

Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, Januzzi JL Jr, Yancy CW. 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. J Am Coll Cardiol. Published online April 19, 2023. https://doi.org/10.1 016/j.jacc.2023.03.393.

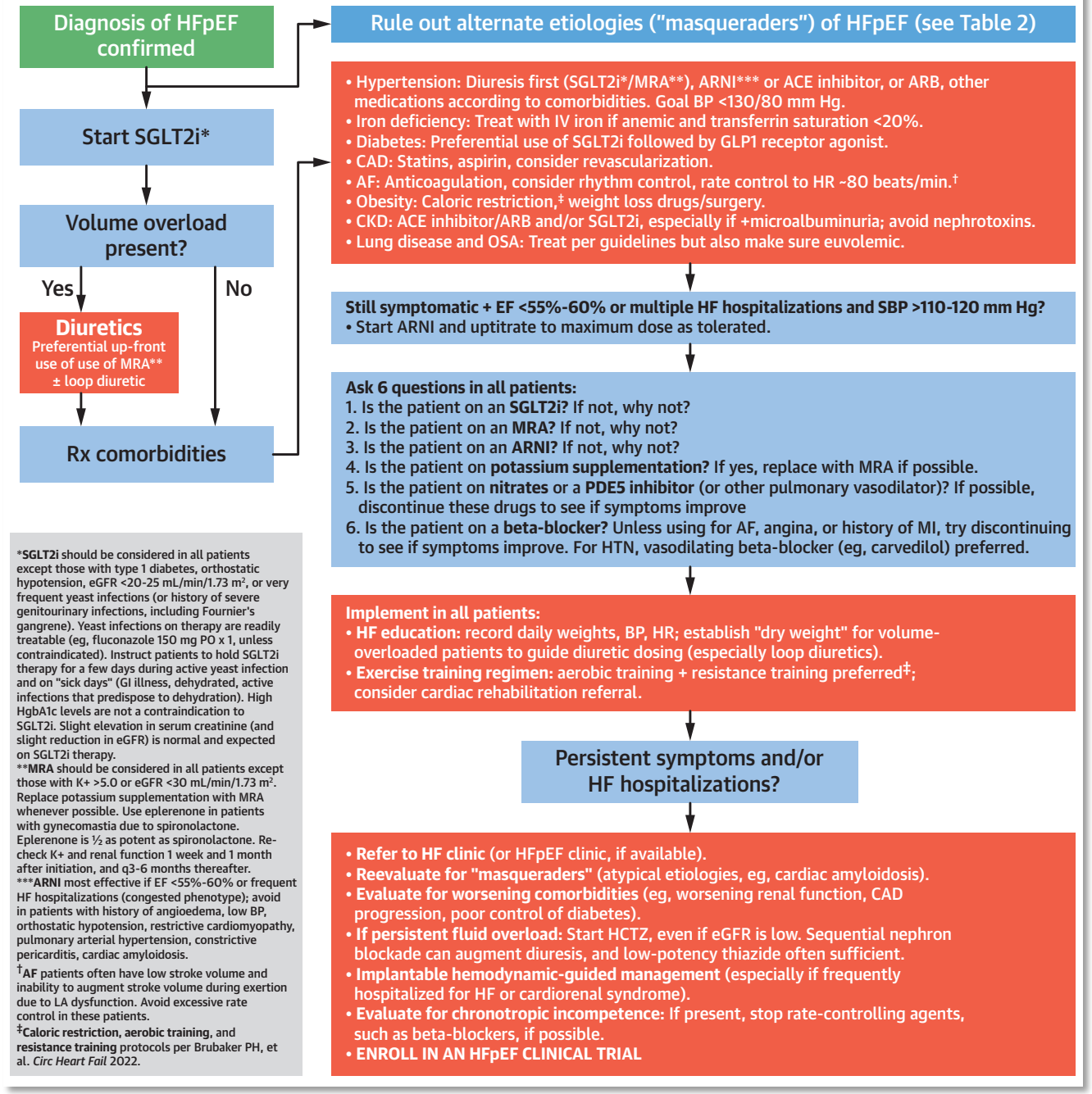
JACC SCIENTIFIC STATEMENT

Heart Failure With Preserved Ejection Fraction

JACC Scientific Statement

Barry A. Borlaug, MD,[a] Kavita Sharma, MD,[b] Sanjiv J. Shah, MD,[c] Jennifer E. Ho, MD[d]

FIGURE 8 Treatment of HFpEF



*SGLT2i should be considered in all patients except those with type 1 diabetes, orthostatic hypotension, eGFR <20-25 mL/min/1.73 m^2, or very frequent yeast infections (or history of severe genitourinary infections, including Fournier's gangrene). Yeast infections on therapy are readily treatable (eg, fluconazole 150 mg PO x 1, unless contraindicated). Instruct patients to hold SGLT2i therapy for a few days during active yeast infection and on "sick days" (GI illness, dehydrated, active infections that predispose to dehydration). High HgbA1c levels are not a contraindication to SGLT2i. Slight elevation in serum creatinine (and slight reduction in eGFR) is normal and expected on SGLT2i therapy.

**MRA should be considered in all patients except those with K+ >5.0 or eGFR <30 mL/min/1.73 m^2. Replace potassium supplementation with MRA whenever possible. Use eplerenone in patients with gynecomastia due to spironolactone. Eplerenone is ½ as potent as spironolactone. Re-check K+ and renal function 1 week and 1 month after initiation, and q3-6 months thereafter.

***ARNI most effective if EF <55%-60% or frequent HF hospitalizations (congested phenotype); avoid in patients with history of angioedema, low BP, orthostatic hypotension, restrictive cardiomyopathy, pulmonary arterial hypertension, constrictive pericarditis, cardiac amyloidosis.

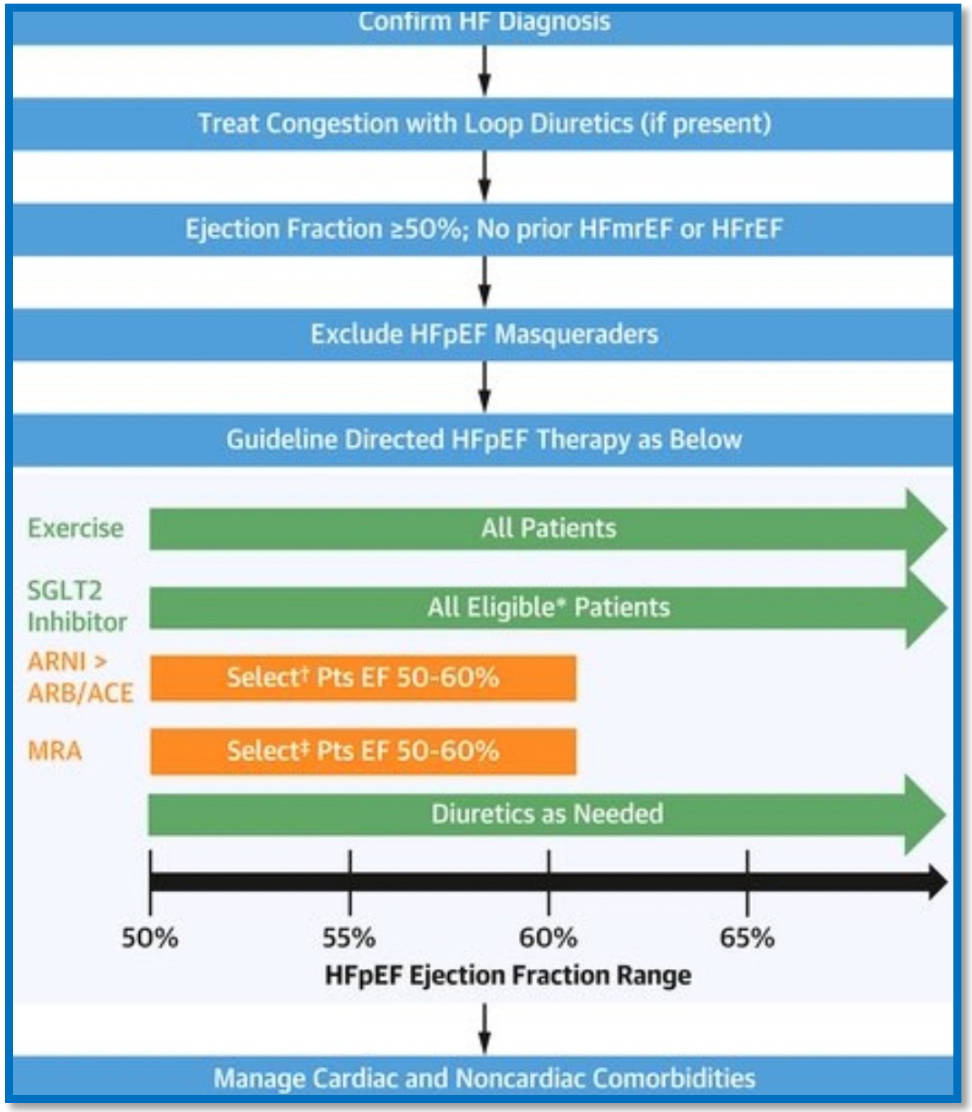
†AF patients often have low stroke volume and inability to augment stroke volume during exertion due to LA dysfunction. Avoid excessive rate control in these patients.

‡Caloric restriction, aerobic training, and resistance training protocols per Brubaker PH, et al. *Circ Heart Fail* 2022.

How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians GET ACCESS

State-Of-The-Art Paper

Akshay S. Desai, Carolyn S.P. Lam, John J.V. McMurray, and Margaret M. Redfield

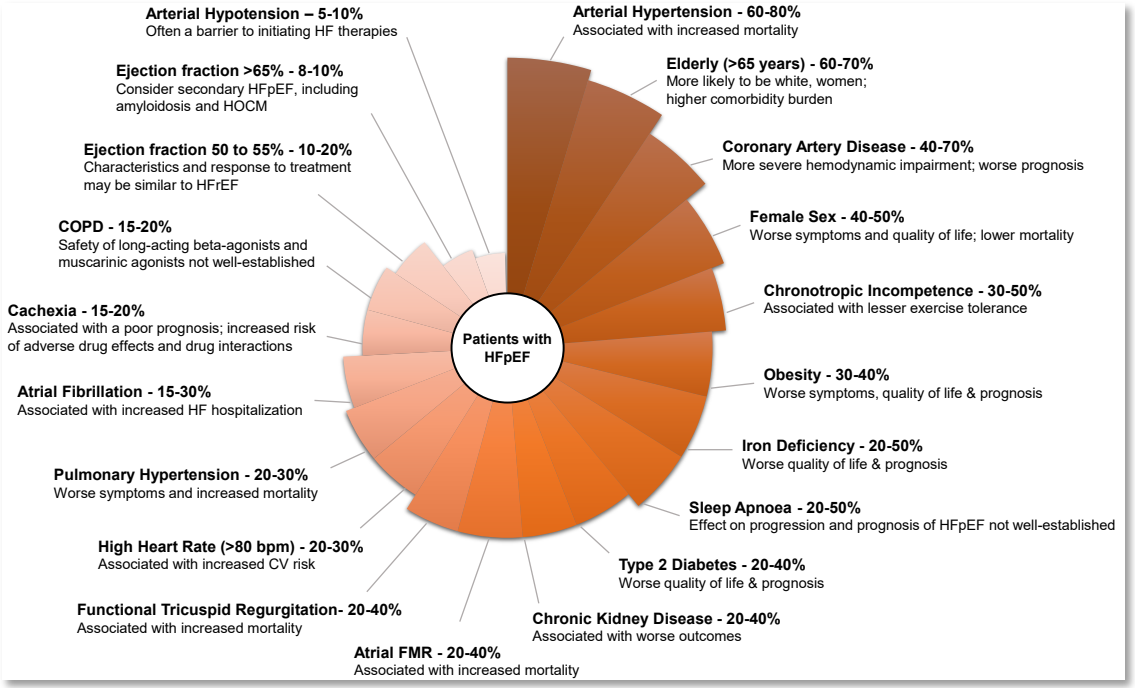


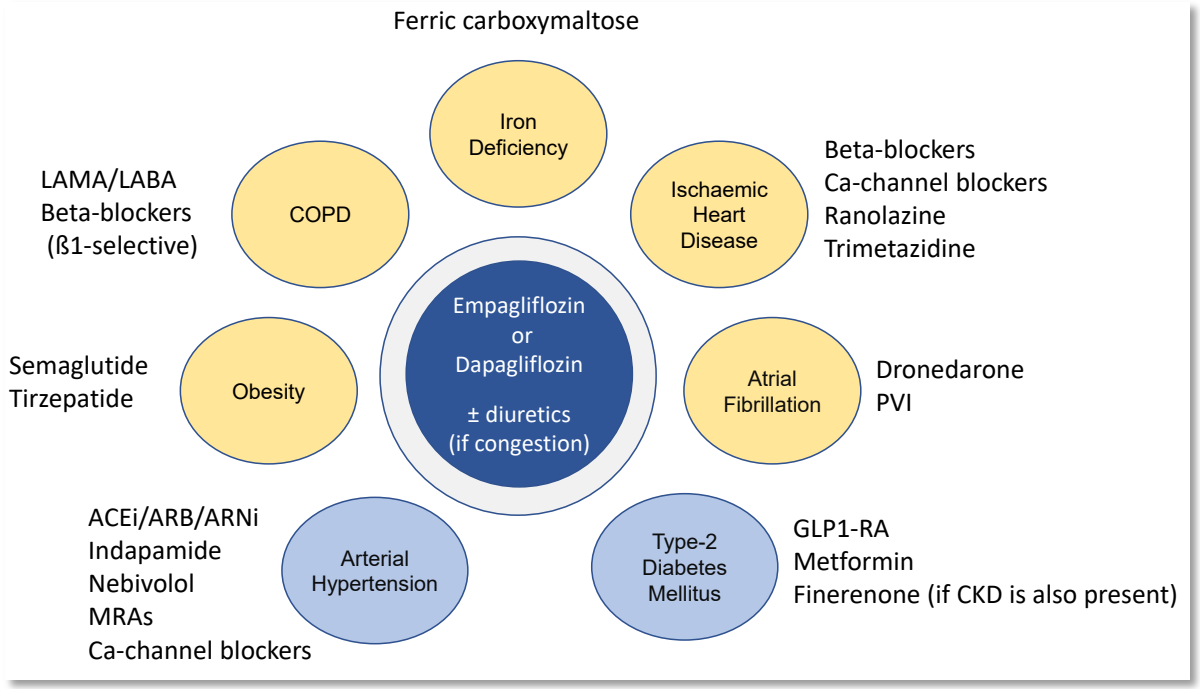
J Am Coll Cardiol HF. *May 03, 2023. Epublished DOI: 10.1016/j.jchf.2023.03.011*

Patient Phenotype Profiling in Heart Failure with Preserved Ejection Fraction

to Guide Therapeutic Decision Making

A Scientific Statement of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the ESC, and the European Society of Hypertension (ESH)





10.1002/ejhf.2894