XXV REUNIÓN

INSUFICIENCIA CARDIACA Y FIBRILACIÓN AURICULAR

4 y 5 mayo 2023 | Palacio de Congresos Girona

#25ICyFA

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

FEMI
FUNDACIÓN ESPAÑOLA DE MEDICINA INTERNA

SEMI Grupo de Insuficiencia Cardiaca y Fibrilación Auricular

Incompetencia cronotropa en IC-FEP y terapia con betabloqueantes

Dr. Pau Llàcer Iborra

Unidad de Insuficiencia Cardiaca (UICA)/UMIPIC

Mercedes, 90 años

HTA, ERC G3bA2, FA permanente, ICC-FEP-CF III NYHA, déficit funcional de hierro con anemia, Obesa (IMC 31)

Barthel 75, Frail 3, Pfeiffer 3 fallos (dependencia moderada, frágil, deterioro cognitivo leve)

En tratamiento: Ramipril 2.5 mg 1c al día, Eplerenona 25 mg 1c desayuno, dapagliflozina 10 mg 1c al día, Bisoprolol 2.5 mg 1c al día, Furosemida 80 mg al día vo, Edoxaban 30 mg al día, fero-gradumet 2c al día.

TA 115/70, FC 68

EVEREST: 7; VExUS: 0; VCI 19, colapsa; LUS: líneas B no significativas

AS: BNP 250 pg/ml (seco 120), Na 134 mmol/L, K 4.8 mmol/L, CKD-EPI 30 ml/min, ACR 550 mg/gr, Hb 11 gr/dl, CA125 38 U/ml (seco 27 U/ml)

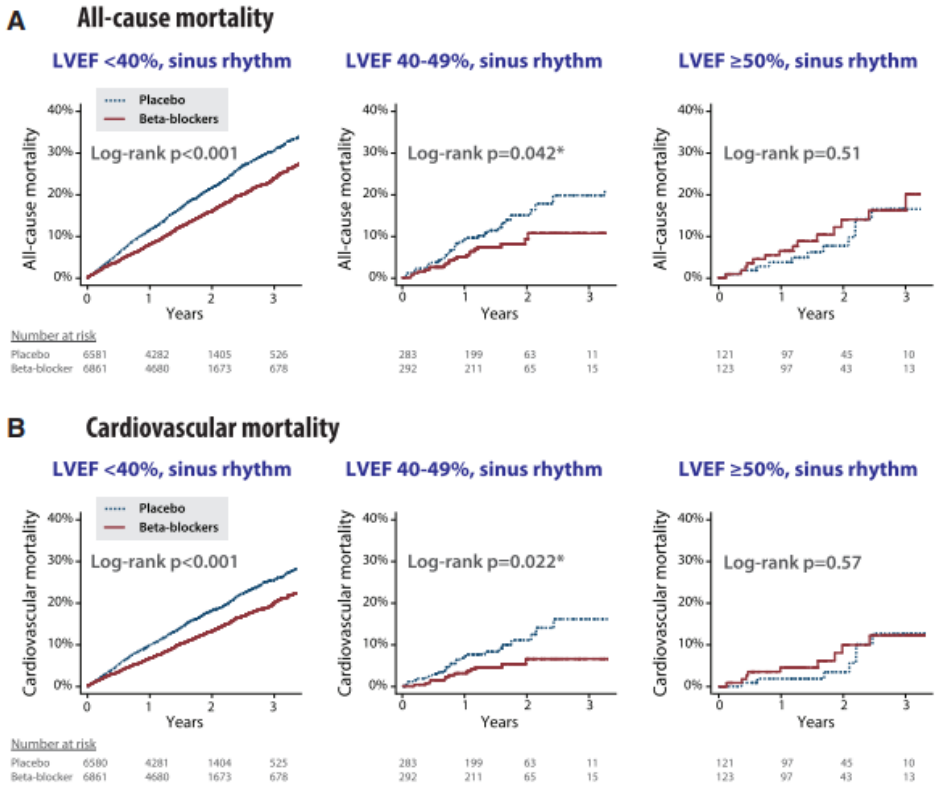
¿Qué podemos hacemos?

Preguntasiiiii

¿Está congestiva?
¿Cómo optizimizamos el tratamiento?
¿Es correcto la utilización de ARM?

¿y el BB?

Background



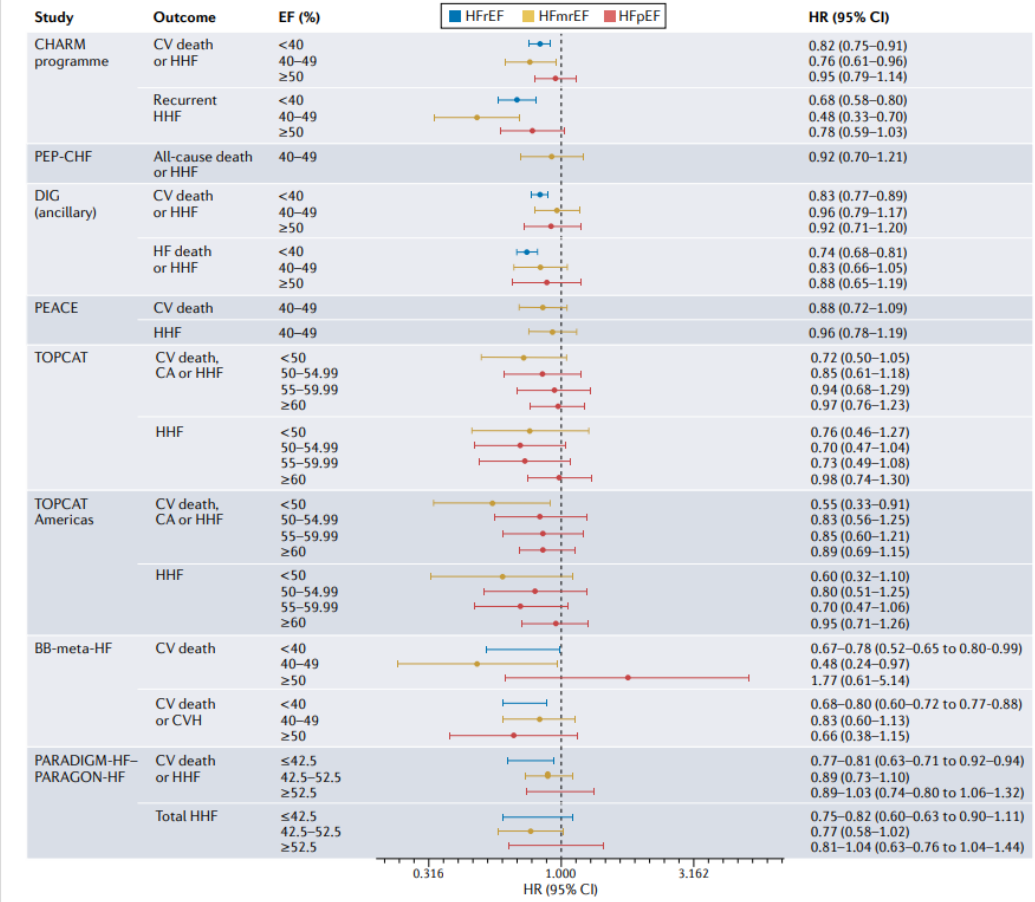
ESC European Society of Cardiology
European Heart Journal (2018) 39, 26–35
doi:10.1093/eurheartj/ehx564
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

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

John G.F. Cleland[1], Karina V. Bunting[2], Marcus D. Flather[3], Douglas G. Altman[4], Jane Holmes[4], Andrew J.S. Coats[5], Luis Manzano[6], John J.V. McMurray[7], Frank Ruschitzka[8], Dirk J. van Veldhuisen[9], Thomas G. von Lueder[10,11], Michael Böhm[12], Bert Andersson[13], John Kjekshus[14], Milton Packer[15], Alan S. Rigby[16], Giuseppe Rosano[17,18], Hans Wedel[19], Åke Hjalmarson[13], John Wikstrand[20], and Dipak Kotecha[2,11]*; on behalf of the Beta-blockers in Heart Failure Collaborative Group

Cleland JGF, et al. Eur Heart J. 2018 Jan l;39(l):26-35.

Background

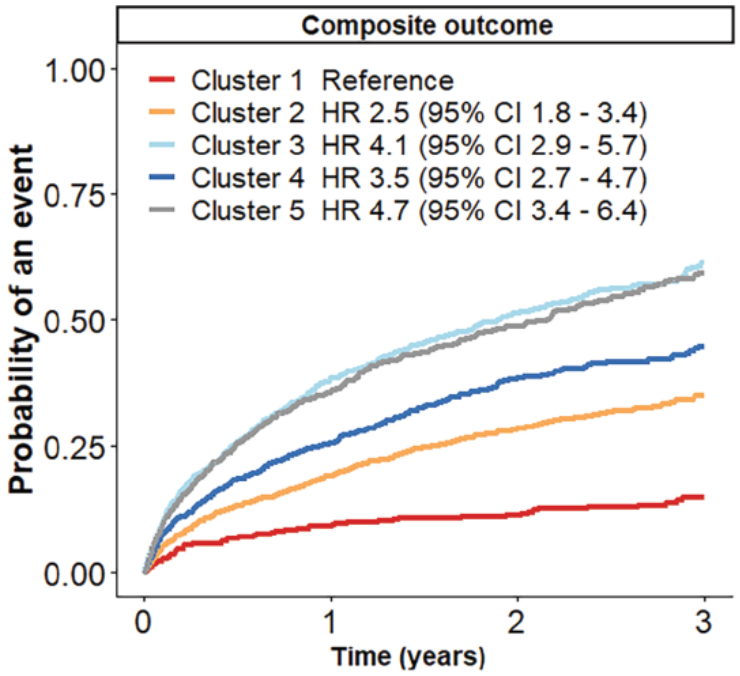


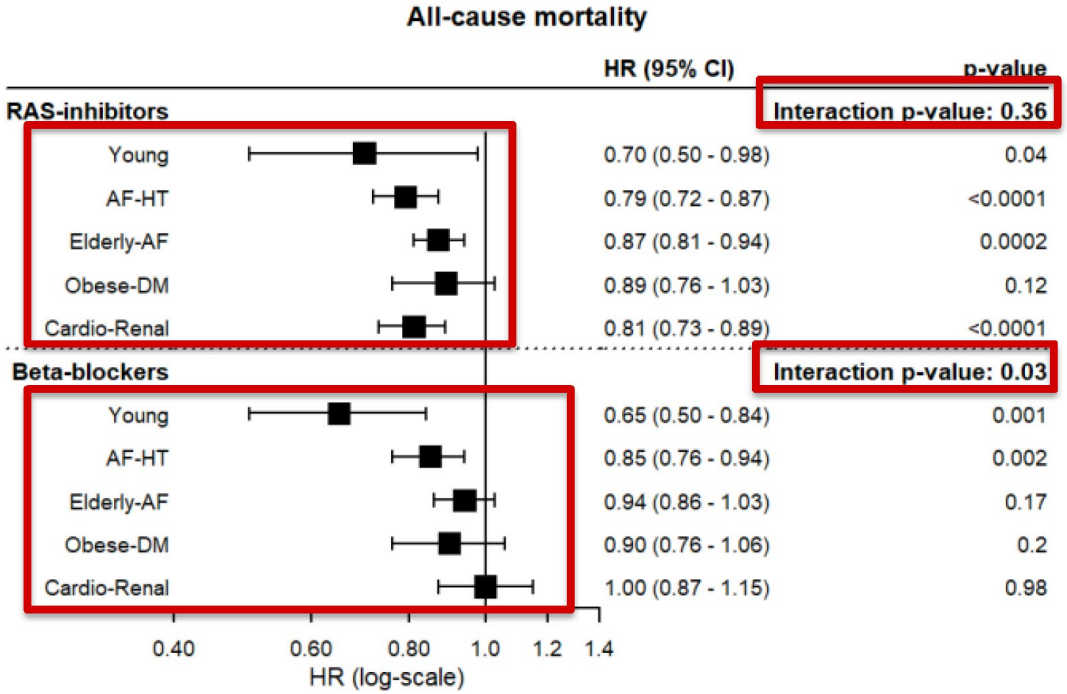
LVEF≥50%
ARA II vs. placebo
CV death/HHF HR 0.95 (0.79-1.14)
ARM vs. placebo
CV death/HHF HR 0.83 (0.56-1.25)
BB vs. placebo
CV death HR 1.77 (0.61-5.14)
ARNI vs. valsartan
CV death/HHF HR 0.89 (0.74-1.06)

Savarese G, et al. Nat Rev Cardiol 2022; 19(2): 100-116

Background

HFpEF →different diseases





1. Uijl A et al. Eur J Heart Fail. 2021 Mar 29
2. Borlaug BA. Nat Rev Cardiol. 2020 Sep;17(9):559-573

Background

En la actualidad, la mayoría de los pacientes con IC-FEP reciben tratamiento con ISRAA o betabloqueantes.
De hecho, en grandes ensayos recientes en IC-FEP, alrededor del **70-80%** de los pacientes recibían β-bloqueantes.

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

TOPCAT
Funded by the NHLBI

Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

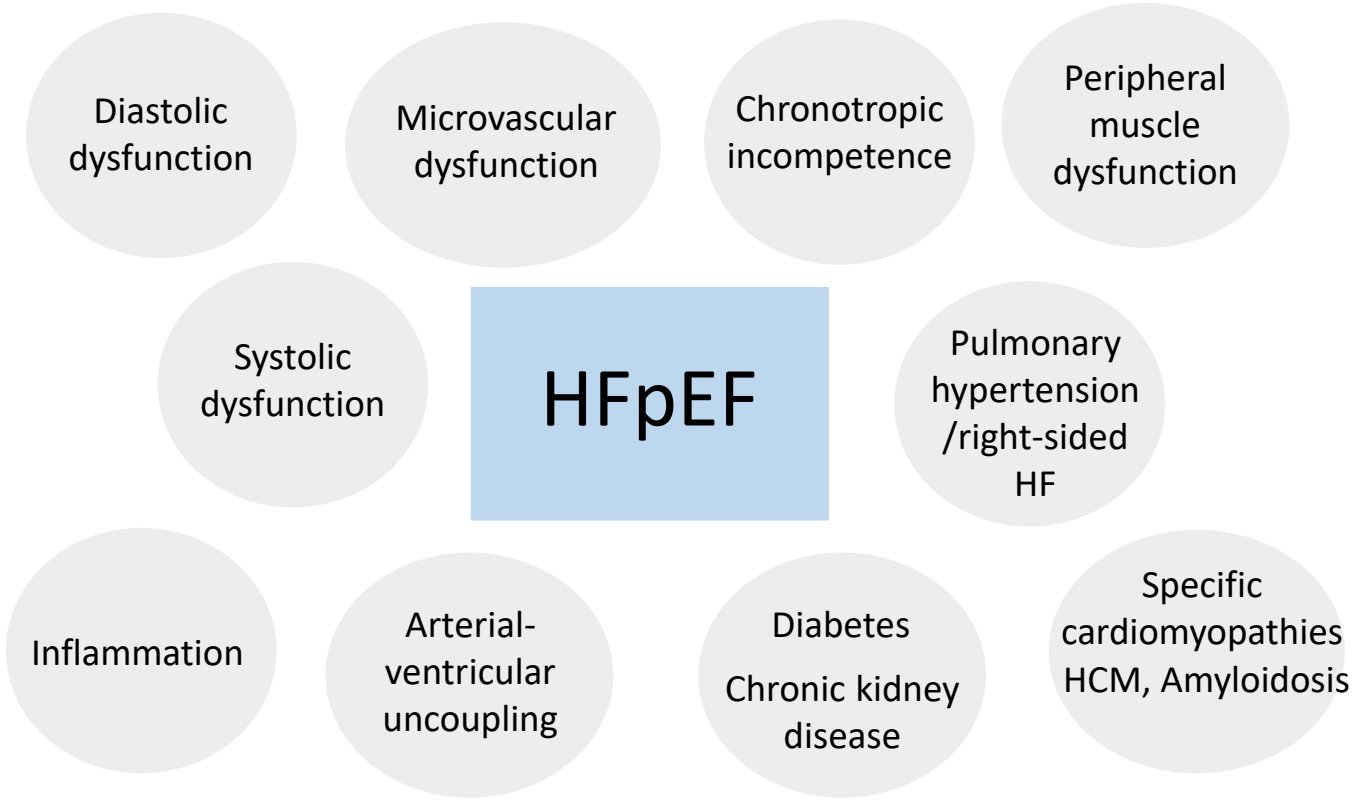
PARAGONHF

>75% de los pacientes estaban tratados con betabloqueantes

1. Pitt B, et al. N Engl J Med. 2014;370:1383-92
2. Solomon SD, et al. N Engl J Med. 2019;381:1609-1620

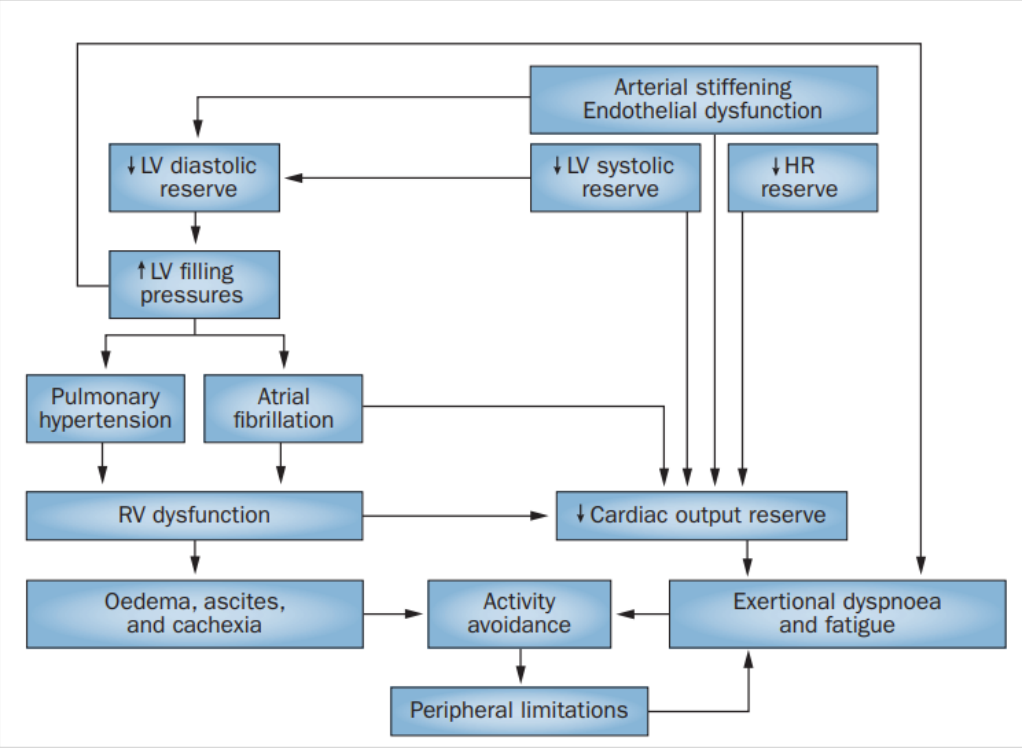
Background

La IC-FEP es un síndrome heterogéneo con varios mecanismos fisiopatológicos subyacentes. Entre ellos, **la incompetencia cronotrópica** ha demostrado desempeñar un papel importante en una gran proporción de estos pacientes.

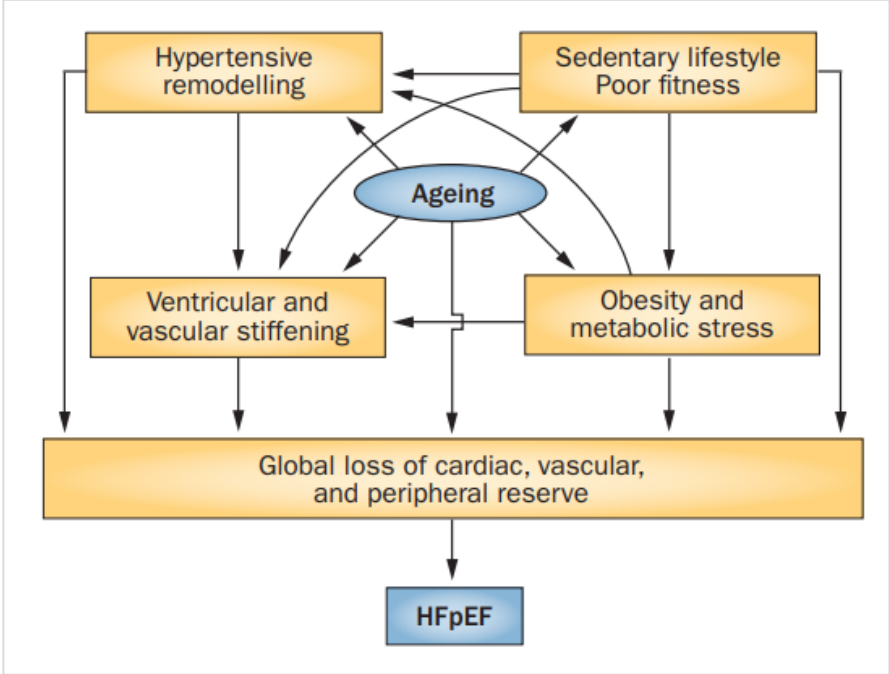


Fisiopatología

Fisiopatología de la IC-FEP



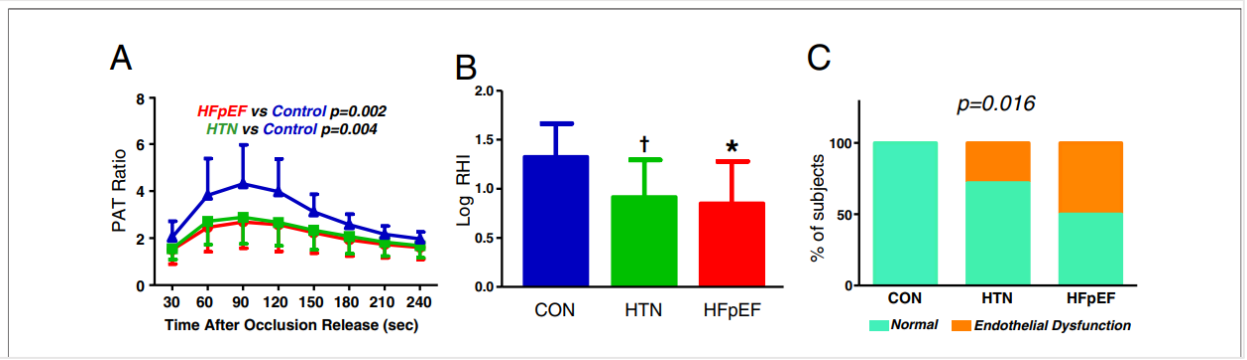
La interacción entre FRCV, el envejecimiento cardíaco y la pérdida de reserva cardiovascular, con en el desarrollo de IC-FEP sintomática



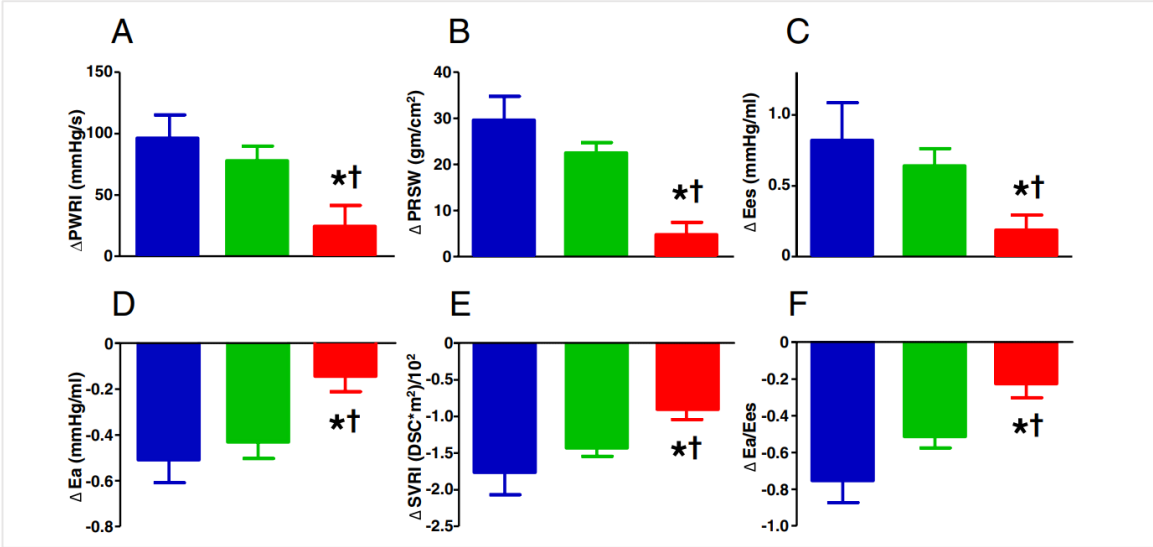
Borlaug BA. Nat Rev Cardiol. 2014 Sep;11(9):507

Fisiopatología

Evaluación de la función endotelial



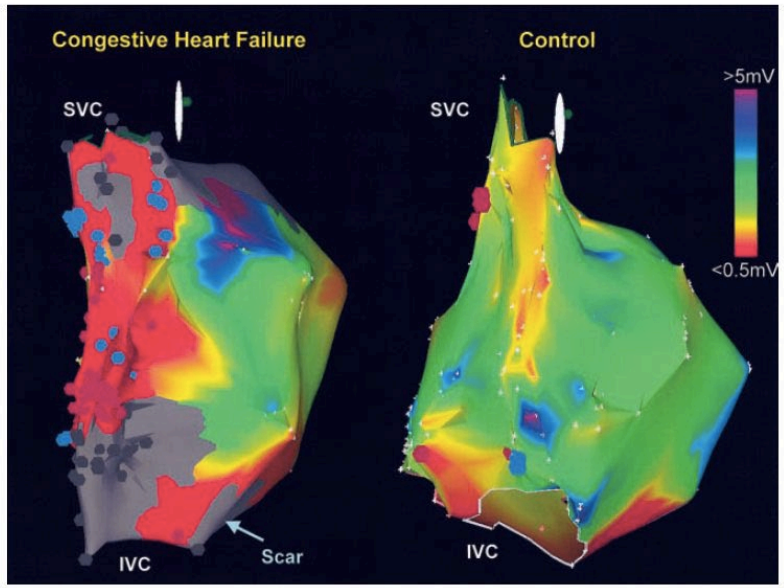
Reserva contráctil, vascular y de acoplamiento con ejercicio de bajo nivel (20 W)

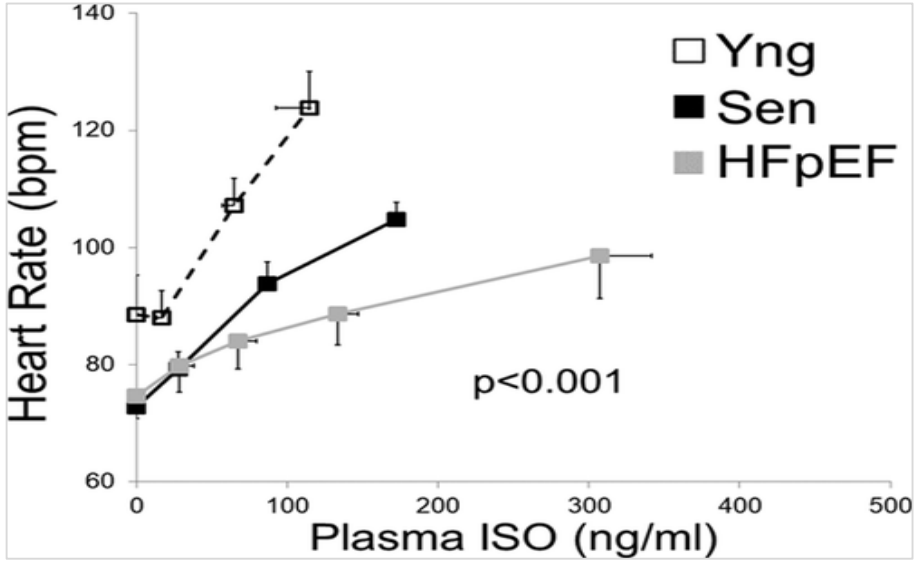


Comparados con los controles emparejados en función de la edad, el sexo y las comorbilidades, los pacientes con IC-FEP tienen una capacidad de ejercicio significativamente menor

Borlaug BA, et al. J Am Coll Cardiol. 2010 Sep 7;56(11):845-54

Fisiopatología



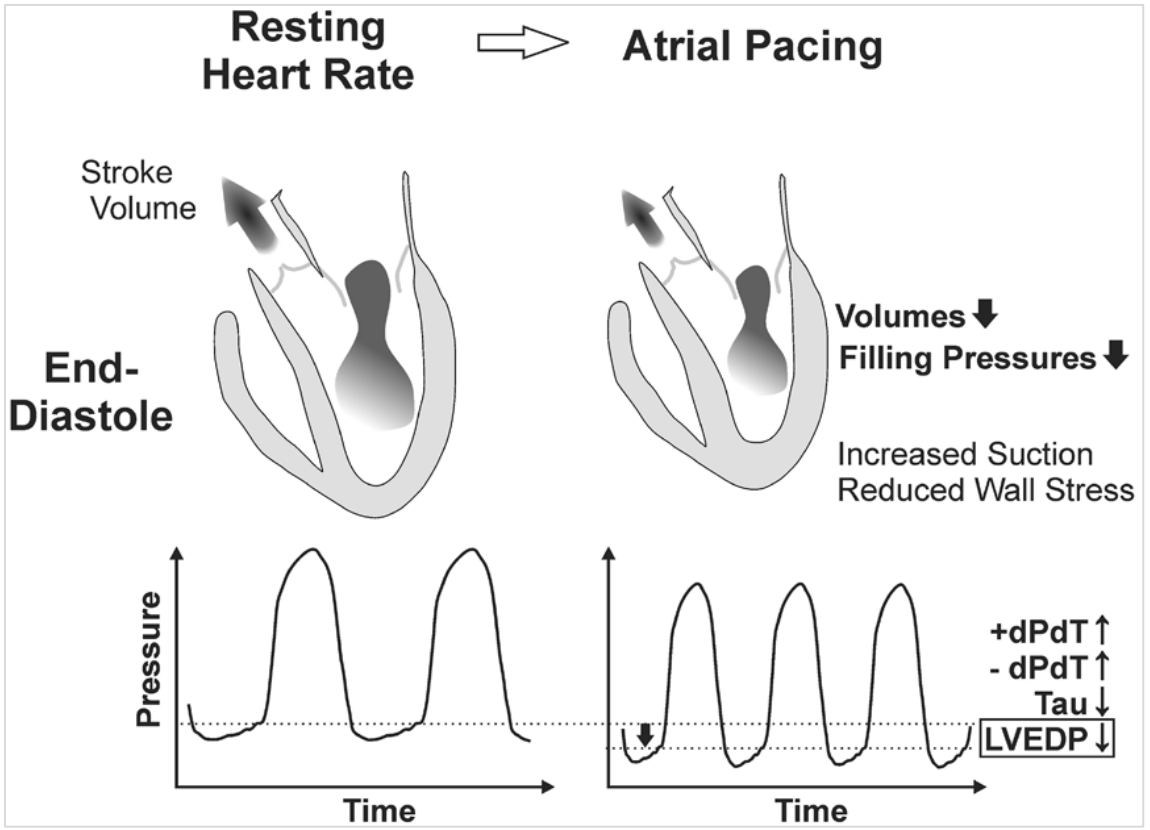


Los pacientes con IC-FEP mostraron una menor sensibilidad de los receptores β cardíacos en comparación con los controles seniors

Satyam S, et al. Circ Heart Fail. 2020 Mar;13(3):e006331.

Consecuencias hemodinámicas de la IC

Chronotropic incompetence in HFpEF



Meyer M, et al. Circ Heart Fail. 2019;12

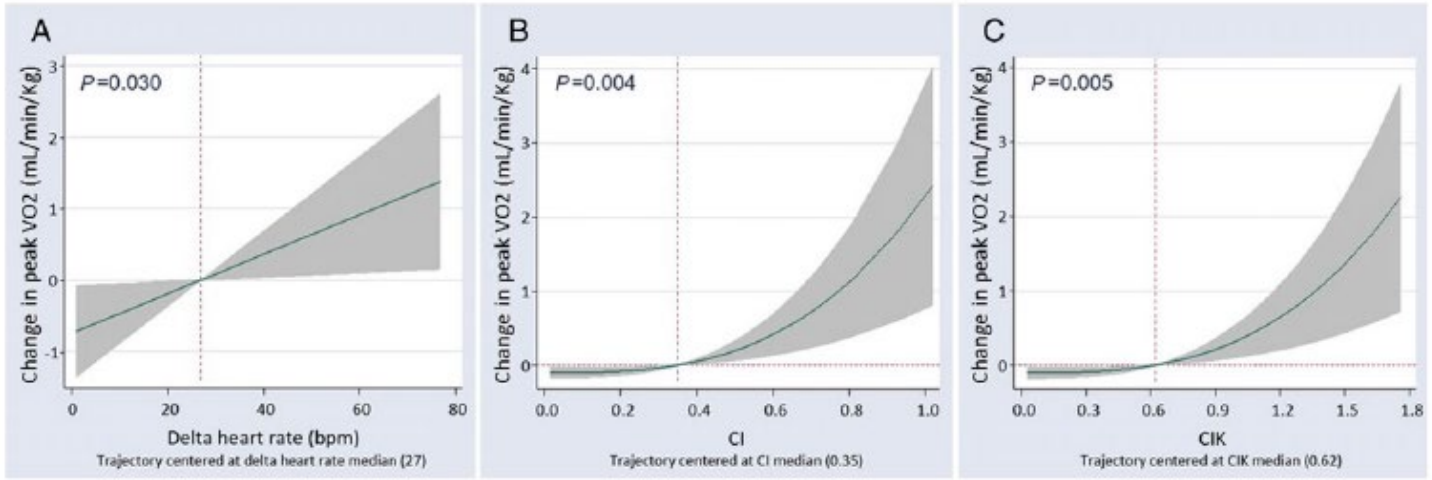
La CI emerge como un mecanismo que contribuye a la limitación de la capacidad funcional para el ejercicio

Consecuencias clínicas de la IC

Chronotropic index (maximum effort heart rate – rest heart rate)/[(220- age) – rest heart rate]:

*Chronotropic incompetence if <0.8 in those without B-blockers

* Chronotropic incompetence if <0.62 with B-blockers



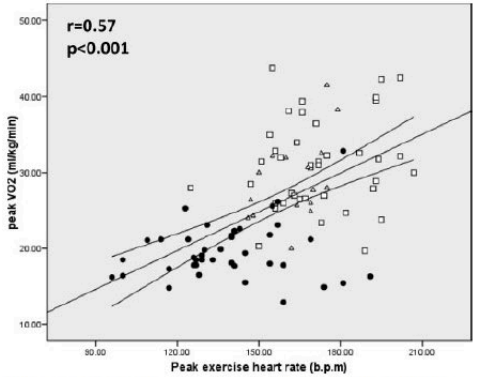
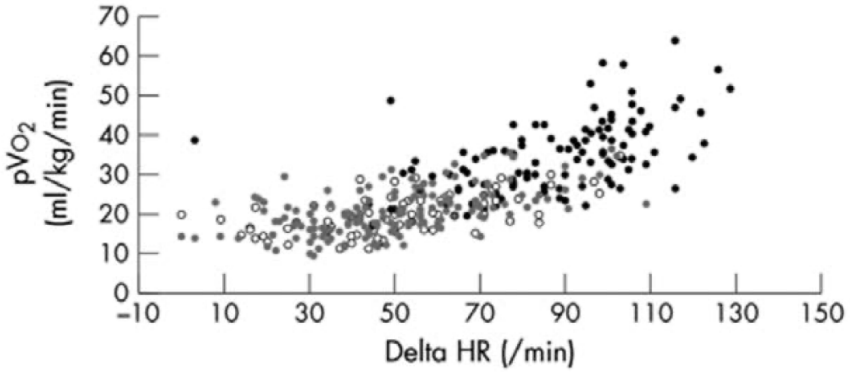


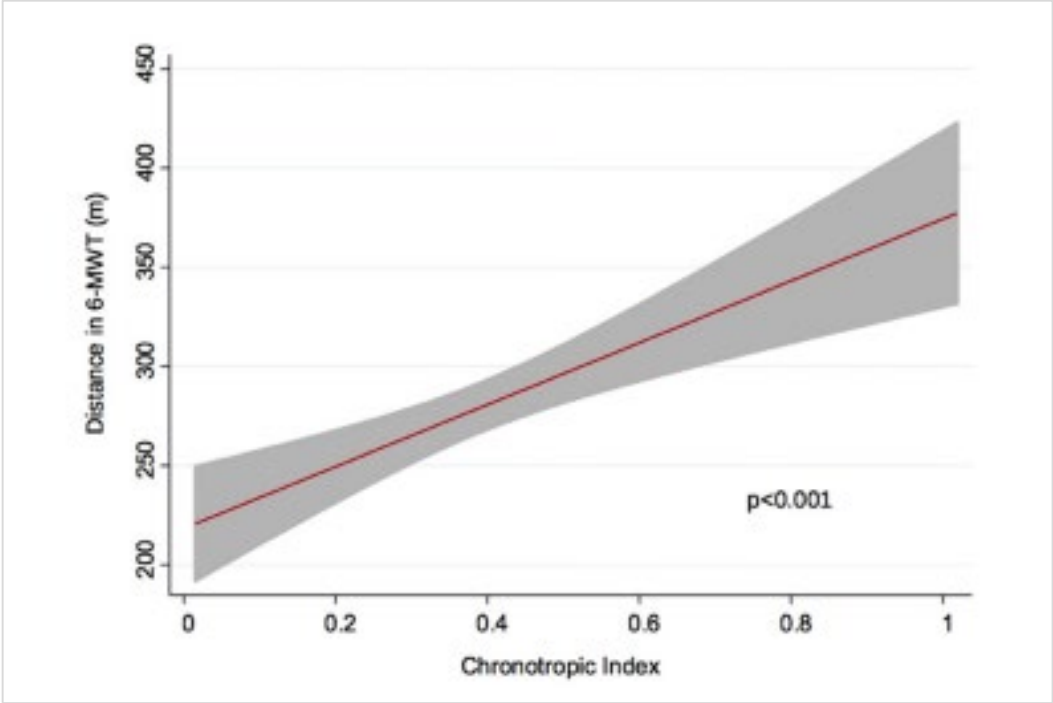
Figure 3. Peak oxygen consumption correlating directly with peak exercise HR. Black dots, patients with HfpEF; triangles, hypertensive controls; and squares, healthy controls.



Dominguez et at. ESC Heart Fail. 2018;5(4):579–585..
Sarma S, et al. Circ Heart Fail. 2020;13:e006331

Consecuencias clínicas de la IC

Chronotropic index and 6MWT in HFpEF



Palau P et al. J Card Fail. 2020;26:1024-1025

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

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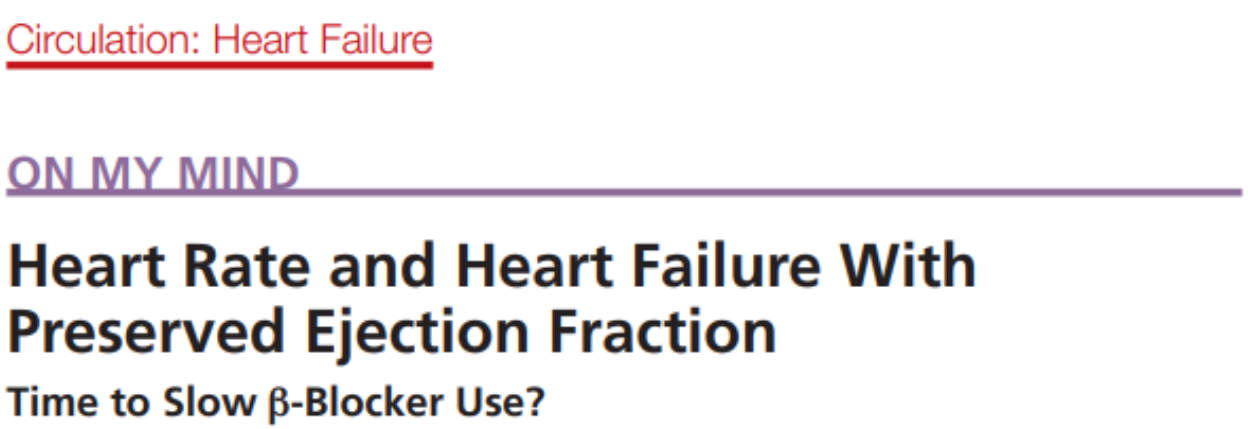
Palau P, et al. J Am Coll Cardiol. 2021 Nov 23;78(21):2042-2056.

Hipótesis


Circulation: Heart Failure

ON MY MIND

Heart Rate and Heart Failure With Preserved Ejection Fraction

Time to Slow β-Blocker Use?

β-Blocker withdrawal in patients with HFpEF and CI will translate into a short-term improvement in functional capacity.

Meyer M, et al. Circ Heart Fail. 2019;12:e006213

Objetives

Primary endpoint

Change from baseline in mean peakVO_2 and percent predicted peakVO_2 (**peakVO_2%**)

Secondary endpoints

(a) Changes in **QoL** assessed by MLHF

(b) Changes in **echocardiogram** parameters (E/e'ratio)

(c) Changes in the **biomarkers**, NT-proBNP**,** and serum carbohydrate antigen 125 (CA125)

(d) Changes in **cognitive function** assessed by MMSE and MoCA

.

Palau, P, et al. Clinical Cardiology. 2020;43:423–429

Study design

Cross-over investigator-blinded randomized clinical trial performed in 2 centers in Spain

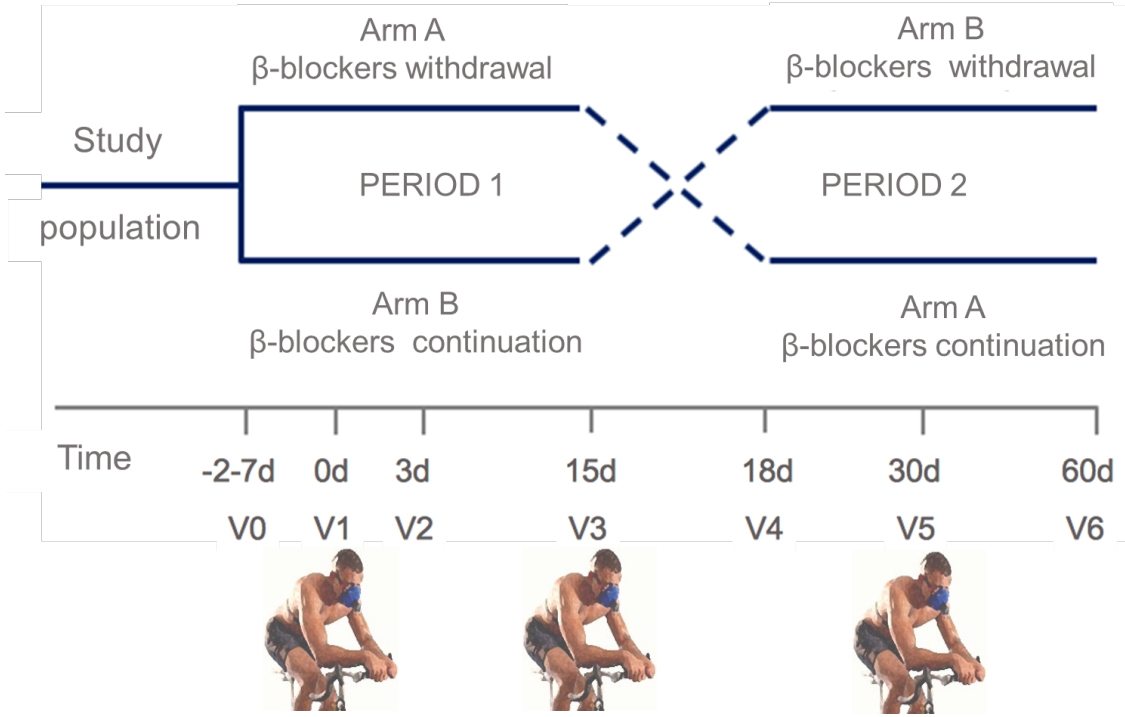
N=52

Inclusion criteria

- Diagnosis criteria of stable HFpEF according to ESC guidelines. (LVEF ≥50%, NT-proBNP >125 pg/ml)
- NYHA ≥II
- Previous admission for AHF.
- Stable treatment with β-blockers during the last 3 months.
- Chronotropic incompetence assessed by CPET*

Exclusion criteria

- Inability to perform a valid baseline exercise test
- Prior history of LVEF <50%
- History of an ACS in the previous 12 months
- Effort angina
- HR at rest >75 bpm

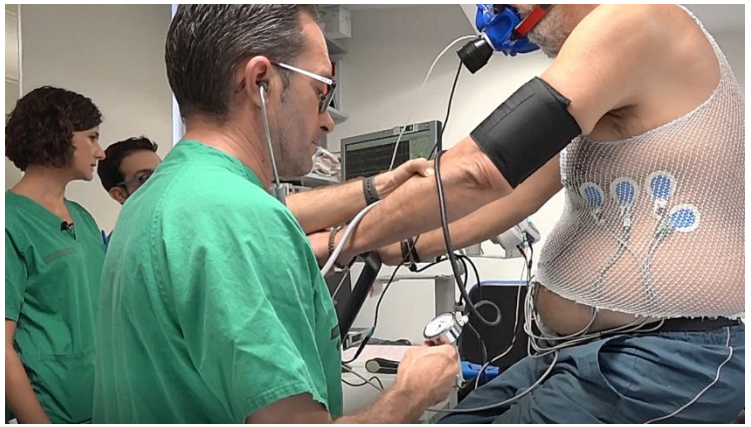


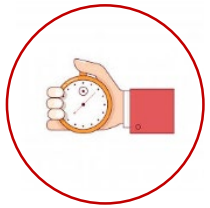
***Chronotropic incompetence definition:**
[(HRmax - HRrest)] / [(220 - age) - (HRrest)] < 0.62

Palau, P, et al. Clinical Cardiology. 2020;43:423–429

Methods

How we defined chronotropic incompetence?





Chronotropic index (maximum effort heart rate – rest heart rate)/[(220- age) – rest heart rate]:

*Chronotropic incompetence if <0.8 in those without B-blockers

* Chronotropic incompetence if <0.62 with B-blockers

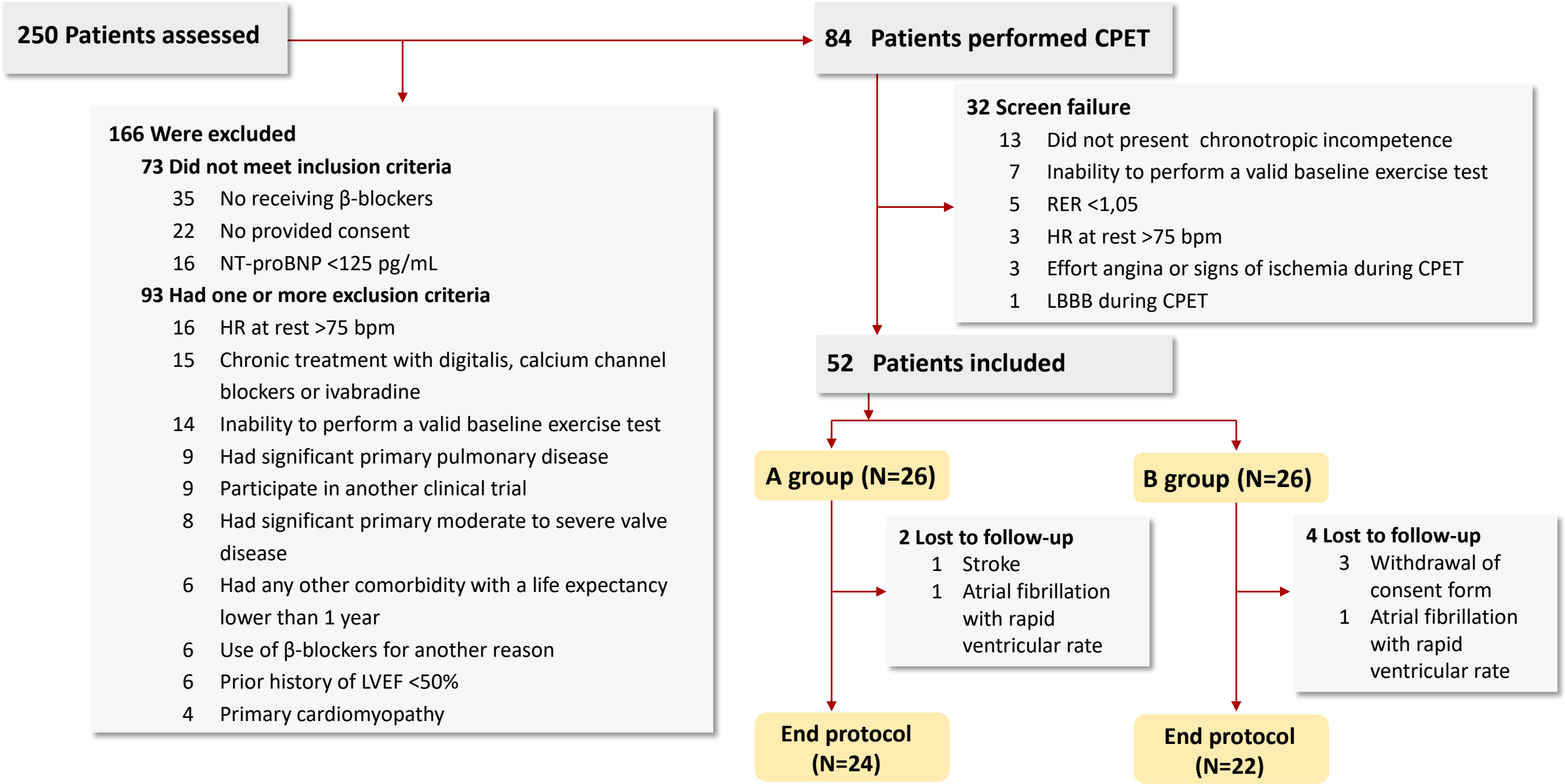
Methods

PROTOCOL: 10W / 1 minute.

RER ≥1.05

Palau P, et al. J Am Coll Cardiol. 2021 Nov 23;78(21):2042-2056.

Flow chart


250 Patients assessed
84 Patients performed CPET
166 Were excluded
73 Did not meet inclusion criteria
35 No receiving β-blockers
22 No provided consent
16 NT-proBNP <125 pg/mL
93 Had one or more exclusion criteria
16 HR at rest >75 bpm
15 Chronic treatment with digitalis, calcium channel blockers or ivabradine
14 Inability to perform a valid baseline exercise test
9 Had significant primary pulmonary disease
9 Participate in another clinical trial
8 Had significant primary moderate to severe valve disease
6 Had any other comorbidity with a life expectancy lower than 1 year
6 Use of β-blockers for another reason
6 Prior history of LVEF <50%
4 Primary cardiomyopathy
32 Screen failure
13 Did not present chronotropic incompetence
7 Inability to perform a valid baseline exercise test
5 RER <1,05
3 HR at rest >75 bpm
3 Effort angina or signs of ischemia during CPET
1 LBBB during CPET
52 Patients included
A group (N=26)
B group (N=26)
2 Lost to follow-up
1 Stroke
1 Atrial fibrillation with rapid ventricular rate
4 Lost to follow-up
3 Withdrawal of consent form
1 Atrial fibrillation with rapid ventricular rate
End protocol (N=24)
End protocol (N=22)

Results
Baseline characteristics

Variables	All patients (N=52)	A-arm (N=26)	B-arm (N=26)	p-value
Demographic and medical history				
Age, years*	74.5 (68.5-79.5)	73 (68-77)	76.5 (72-80)	0.101
Women	31 (59.6)	14 (53.9)	17 (65.4)	0.572
BMI, kg/m^2	31.1±4.7	30.9±5.3	31.3±4.0	0.741
Hypertension	46 (88.5)	22 (84.6)	24 (92.3)	0.668
Diabetes	21 (40.4)	9 (34.6)	12 (46.2)	0.572
Dyslipidemia	37 (71.2)	16 (61.5)	21 (80.8)	0.132
Prior history of IHD	12 (23.1)	7 (26.9)	5 (19.2)	0.743
NYHA III/IV	18 (34.6)	8 (30.8)	10 (38.5)	0.771
Vital signs at rest				
HR, BPM	64.8 ±8.8	64.9±10.8	64.8±8.8	0.531
SBP, mmHg	123.4±16.8	124.5±14.2	122.4±16.8	0.637
DBP, mmHg	65.6±8.4	64.2±8.0	67.1±8.7	0.225
Echocardiographic and ECG parameters				
LVEF, %	64.7±7.1	63.8±7.1	65.7±7.0	0.338
Atrial fibrillation	10 (19.2)	7 (26.9)	3 (11.5)	0.291
Laboratory values				
Hb, g/dL	13.3±1.4	13.4±1.7	13.1±1.1	0.459
eGFR, mL/min/1.73m$_2$	64.7±21.2	67.2±23.5	62.2±18.8	0.399
NT-proBNP, pg/mL*	400 (205-1039)	424 (234-1294)	344.5 (204-662)	0.341

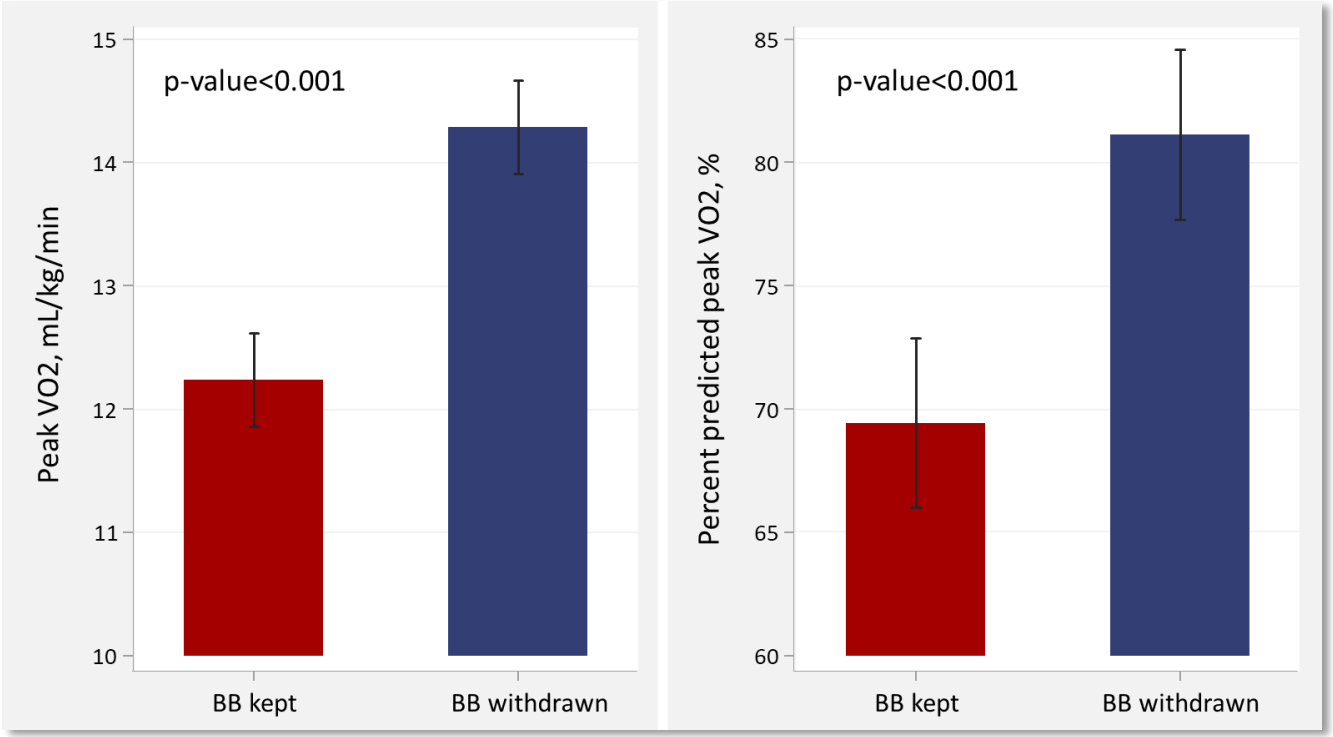
Variables	All patients (N=52)	A-arm (N=26)	B-arm (N=26)	p-value
Cardiopulmonary exercise testing variables				
PeakVO_2, mL/kg/min	12.4±2.9	12.2±2.9	12.5±2.9	0.687
Percent predicted PeakVO_2	72.4±17.8	67.6±17.9	77.2±16.6	0.051
VE/VCO_2 slope	33.7±5.4	34.1±5.7	33.4±5.1	0.644
RER*	1.2 (1.1-1.3)	1.1 (1.1-1.3)	1.2 (1.1-1.3)	0.581
Chronotropic index	0.41±0.14	0.40±0.13	0.41±0.16	0.842
HR at peak exercise, bpm	97.2±14.7	97.1±15.8	97.3±13.9	0.956
Quality of life and cognitive function variables				
MLHF questionnaire*	26 (11-40)	25 (13-35)	27 (11-40)	0.869
MoCA score	20.7±4.6	21.5±4.0	19.8±5.2	0.219
MMSE score	27.5±2.3	28.0±1.7	27.1±2.7	0.173
Medical treatment				
ACEI or ARB	39 (75)	19 (73.1)	20 (76.9)	0.755
Loop diuretics	44 (84.6)	21 (80.8)	23 (88.5)	0.781
MRA	6 (11.5)	2 (7.7)	4 (15.4)	0.668
Statins	35 (67.3)	18 (69.3)	17 (65.4)	1.000

Continuous variables are presented as mean±ISD, categorical variables as N (%)
* Value expressed as median (IQ)

Primary endpoint

La FC en el pico de ejercicio aumentó significativamente cuando se retiraron los betabloqueantes (least-square means of 127 vs. 97 bpm; p<0.001)

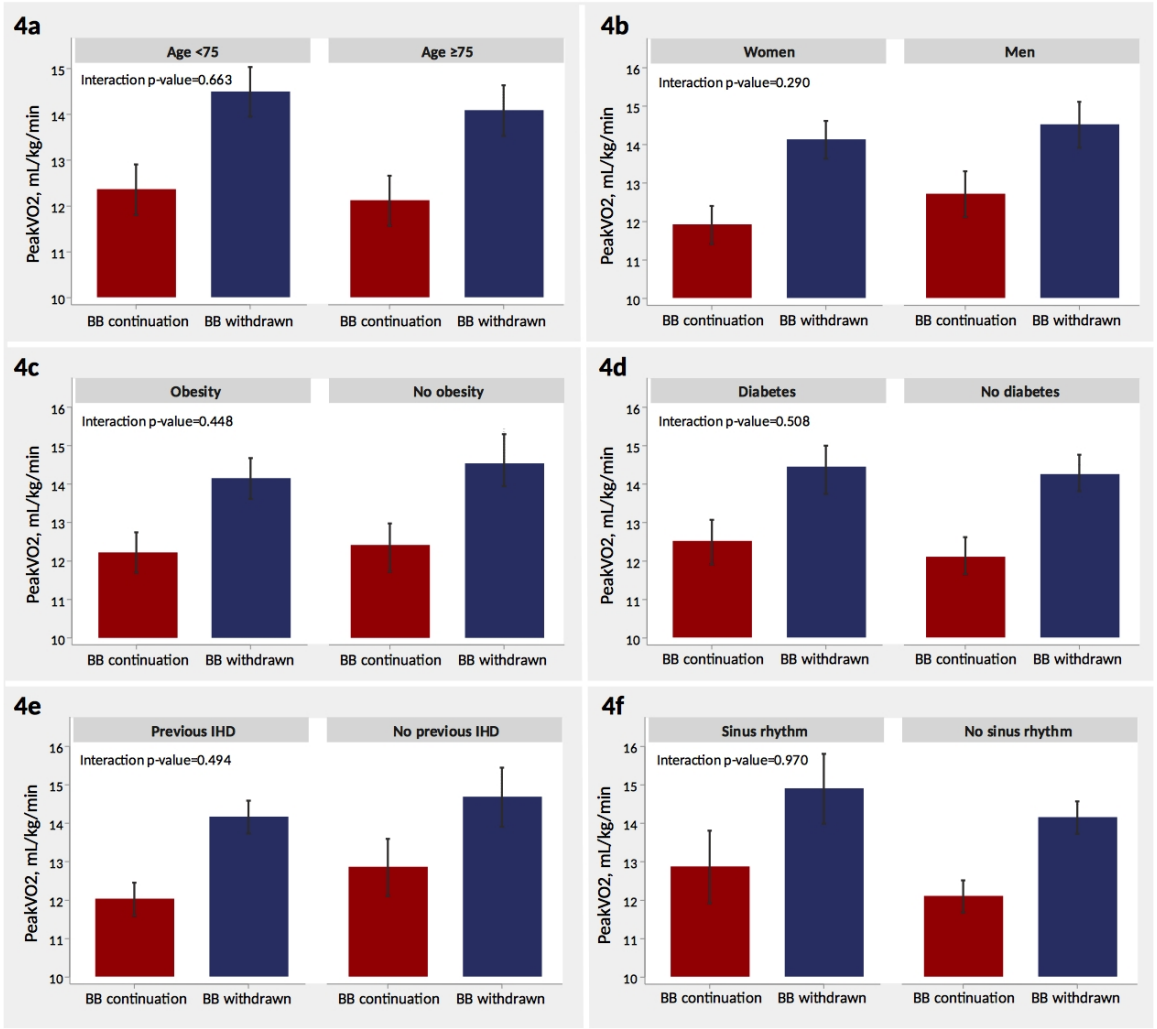
30 bpm



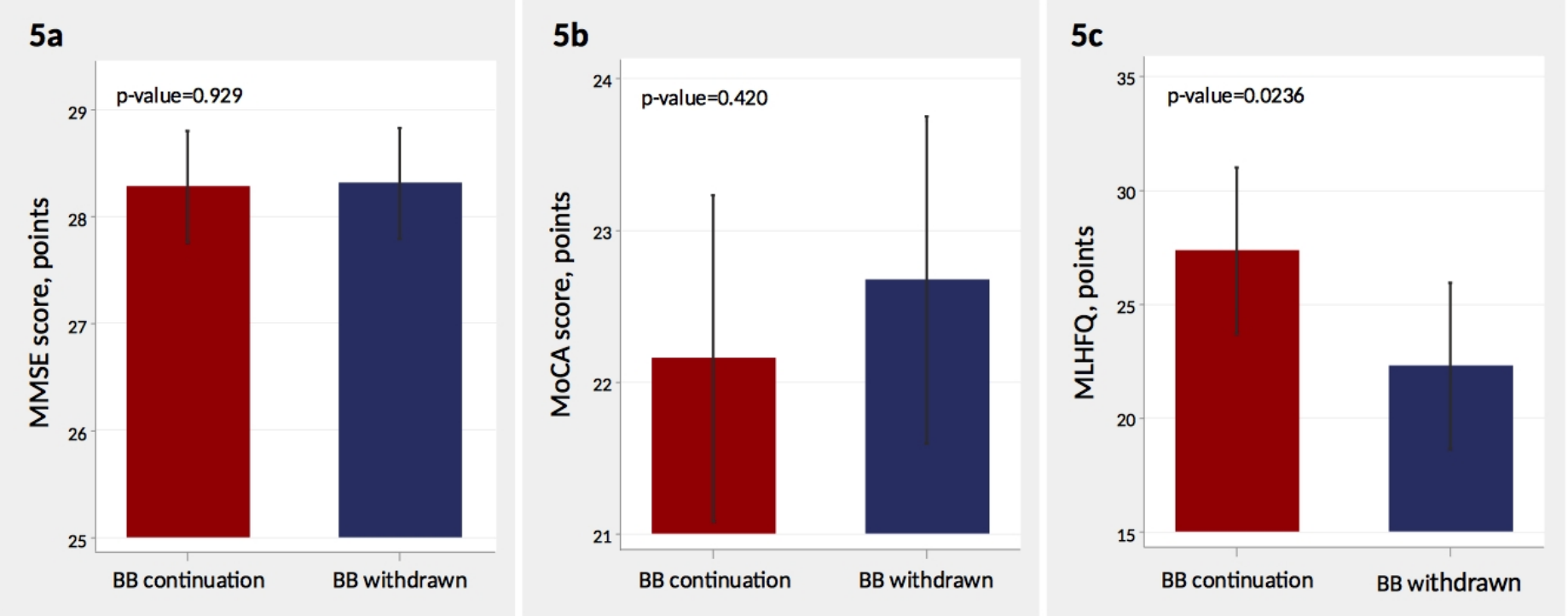
Hubo un aumento significativo del VO2 máximo y del porcentaje de VO2 máximo previsto como resultado de la estrategia de retirada

peak VO2 +2.1 ± 1.29 ml/Kg/min (P < 0.001).
peak VO2% +11.74 ± 2.32 (P < 0.001).

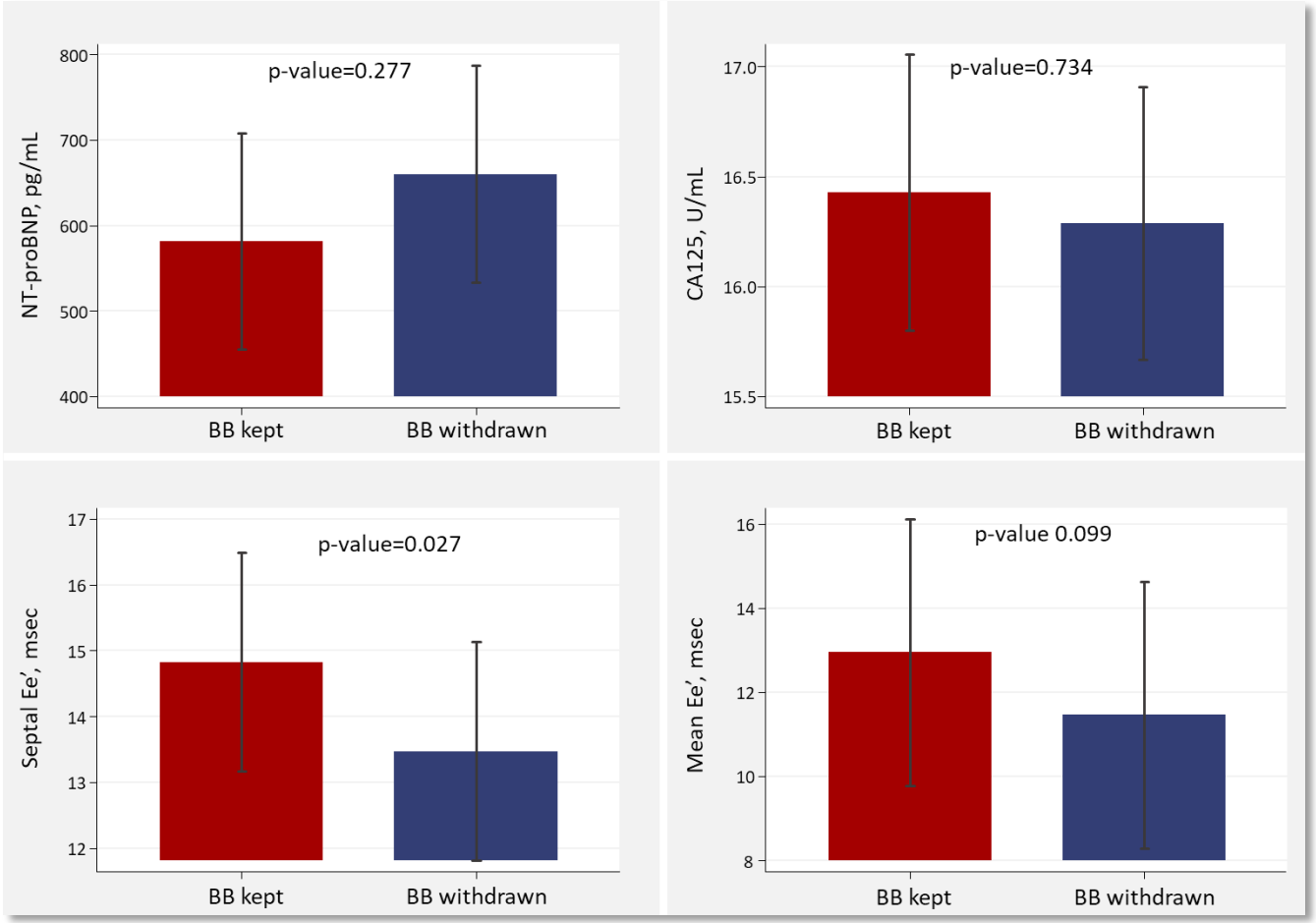
Subgroup analysis



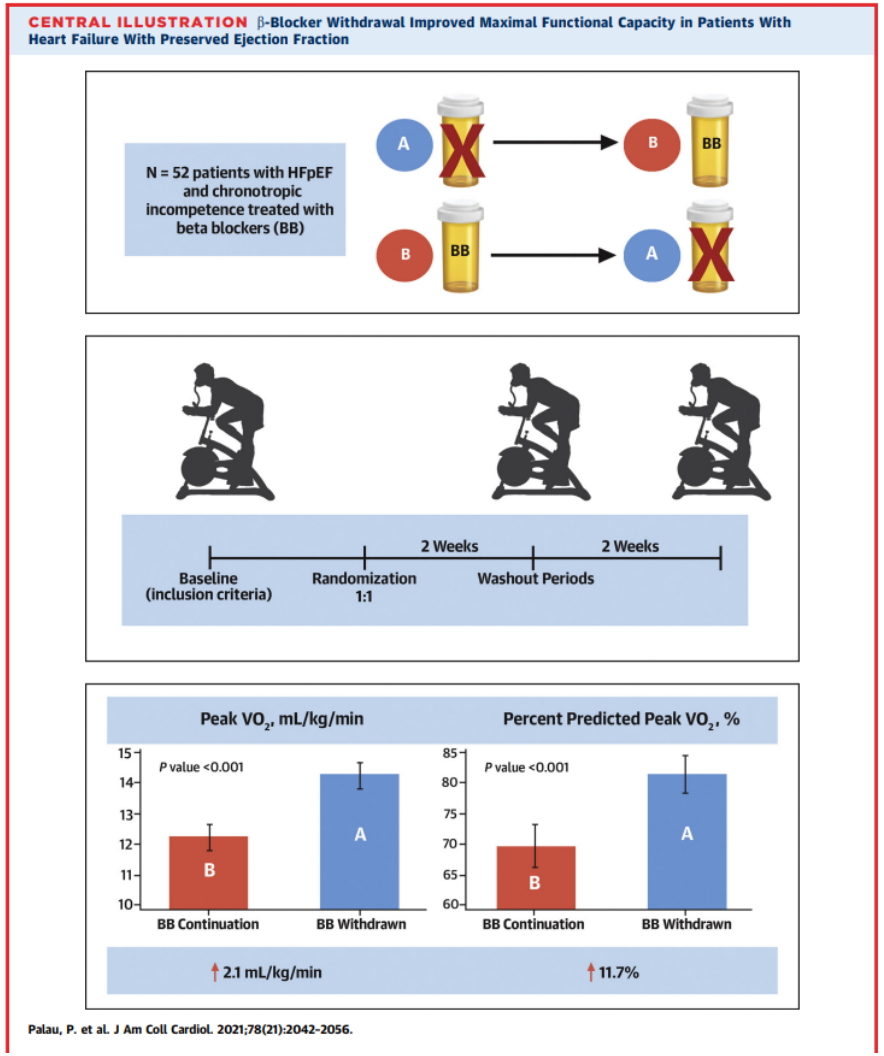
Secondary endpoints



Secondary endpoints

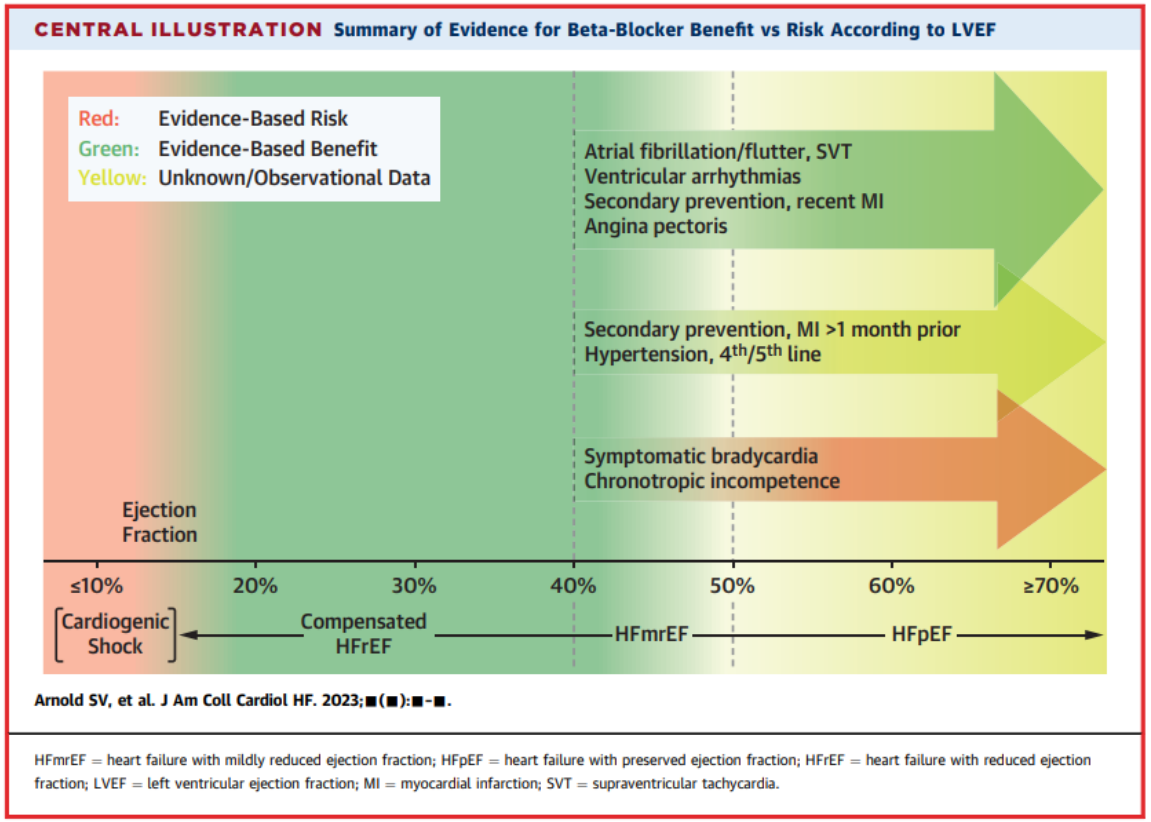


Preserve-HR



Palau, P. et al. J Am Coll Cardiol. 2021;78(21):2042-2056.

¿ Para qué pacientes se podrían reservar entonces los BB?



Mercedes

Una vez se recuperó la euvolemia tras incrementar tratamiento depletivo

Ergoespirometría

6MWT

Un esfuerzo que le produzca disnea

FC en torno a 90 lpm a pesar del esfuerzo (C.Index=0.5)

Retirada del betabloqueanteii

Conclusiones

- Ampliamente extendido el uso de BB en IC-FEP con escasa evidencia
- Fisiopatología compleja de la IC-FEP con papel relevante de la I.cronotropa
- Preserve-HR: en pacientes con IC-FEP estable e I.cronotropa, la retirada de los BB produjo una mejoría sustancial a corto plazo de la VO2 máxima.
- Otros estudios deberán confirmar los resultados actuales y evaluar la seguridad y eficacia clínicas a medio y largo plazo de esta estrategia en la IC-FEP
- BB en fibrilación auricular con FC elevadas, TSV, IAM reciente, angina