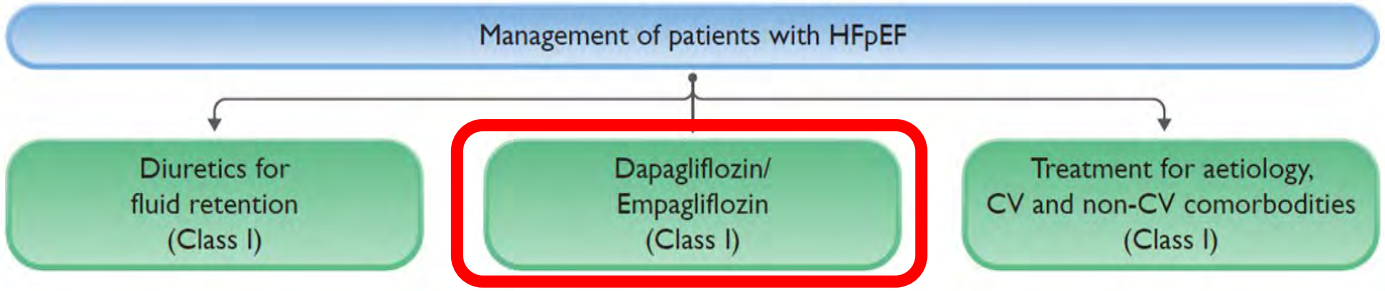
FEVE preservada. Diürètics o alguna cosa més?



DELIVER trial #ESCCongress

Dapagliflozin in heart failure with mildly reduced and preserved ejection fraction

Conclusion

Dapagliflozin reduces the risk of CV death or worsening heart failure (HF) in HF patients with mildly reduced and preserved ejection fraction (EF).

Impact on clinical practice

Taken together with previous research in HF with reduced EF, these data suggest that dapagliflozin is effective regardless of EF and support the use of SGLT2 inhibitors as foundational therapy in all HF patients.

Study objectives

DELIVER examined whether dapagliflozin would decrease CV morbidity and mortality in HF patients with mildly reduced or preserved EF, a group for whom limited therapies are available.

Where?

20 countries

353 sites

Median follow-up ····► 2.3 years

Who and what?

Population

- Patients ≥ 40 years with symptomatic HF with EF > 40% who were either chronic outpatients, hospitalised or recently hospitalised, including those who previously had an EF ≤ 40% (i.e. HF with improved EF)

6,263 patients randomised

- Dapagliflozin 10 mg once daily
- Placebo

Primary outcome

Composite of CV death or worsening HF

Rate%

16.4%

19.5%

Hazard Ratio 0.82
95% CI 0.73–0.92; p<0.001

Key secondary outcome

Total HF hospitalisations and CV death reduced with

versus

Rate Ratio 0.77
95% CI 0.67–0.89

ESC

EMPEROR-PRESERVED

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker et al, Aug 27, 2021. NEJM.

CARDIO NERDS

QUESTION

In patients with heart failure and a preserved ejection fraction, does Empagliflozin improve outcomes?

INCLUDED

- 18 and older
- NYHA II-IV
- LVEF > 40%
- ntProBNP>300; or>900 if AFib
- Evidence of LAE or LVH
- Stable diuretic use
- BMI <45 kg/m2

5988 PATIENTS

EMPAGLIFLOZIN 10MG (SGLT-2 INHIBITOR) vs PLACEBO

Stratified by region, diabetes status, eGFR of 50, and LVEF 50%

PRIMARY OUTCOME

CV Death* HF Hospitalization

13.8%

17.1%

HR 0.79; 95%CI 0.69-0.90; P<0.001

*Mostly driven by HF hospitalizations

SECONDARY OUTCOMES

HF Hospitalization

↓ WITH EMPAGLIFLOZIN

HR 0.73; 95% CI, 0.61-0.88; P<0.001

Rate of GFR decline

E -1.25 vs. -2.62 P

ml/min/1.73m2/year; P<0.001

CONCLUSION

Empagliflozin reduced the combined risk of cardiovascular death or heart failure hospitalization in patients with heart failure with preserved ejection fraction, regardless of the presence or absence of diabetes.

@IsaMathiasMD

2 TRATAMIENTO FARMACOLÓGICO

Diuréticos

1ª LÍNEA

iSGLT2*
(Empagliflozina o
Dapagliflozina 10 mg/d)

¿Persisten síntomas?

2ª LÍNEA

ARM

Sacubitrilo/ Valsartán

β-BLOQUEANTES

Si congestión

- Diuréticos del asa
- Valorar añadir hidroclorotiazida** si ≥80 mg/d de furosemida y persistencia de congestión

Si FEVI <60 %, K+ <5 meq/l, FGe >30 ml/min, Cr <2,5 mg/dl

- Si FEVI ≤60 %***
- Valorar ARA-II (Candesartán) si intolerancia a ARNI o imposibilidad de financiación

EVITAR
Excepto:
- Fibrilación auricular
- IAM reciente
- Angina

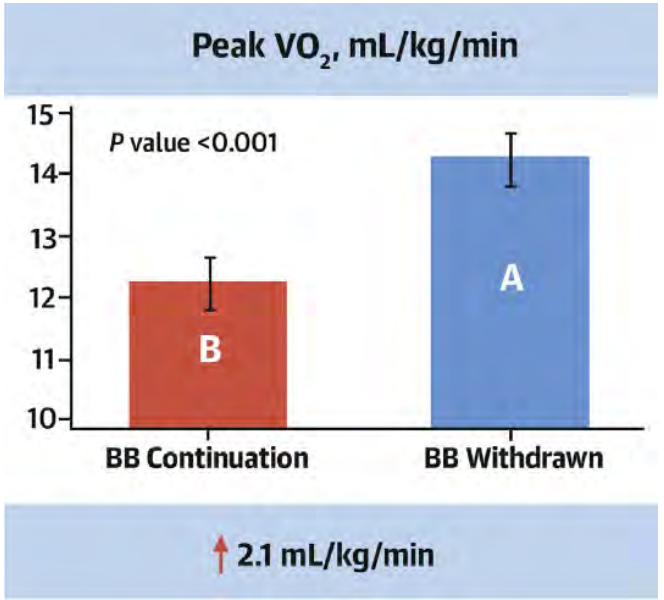
*Excepto DM tipo 1, historia de cetoacidosis diabética o FGe <20 ml/min/1,73 m² para Empagliflozina y <25 ml/min/1,73 m² para Dapagliflozina ensayos EMPEROR-Preserved (Empagliflozina) y DELIVER (Dapagliflozina). **Evidencia en fase aguda con ensayo CLOROTIC con dosis ajustada según FGe. Monitorizar precozmente función renal e iones. ***Análisis conjunto PARAGON-HF y PARAGLIDE-HF.

Proposta grup IC-SEMI:

"Rascar" les evidències post-hoc en **FE 50 - 60%** d'assajos amb espironolactona i S/V

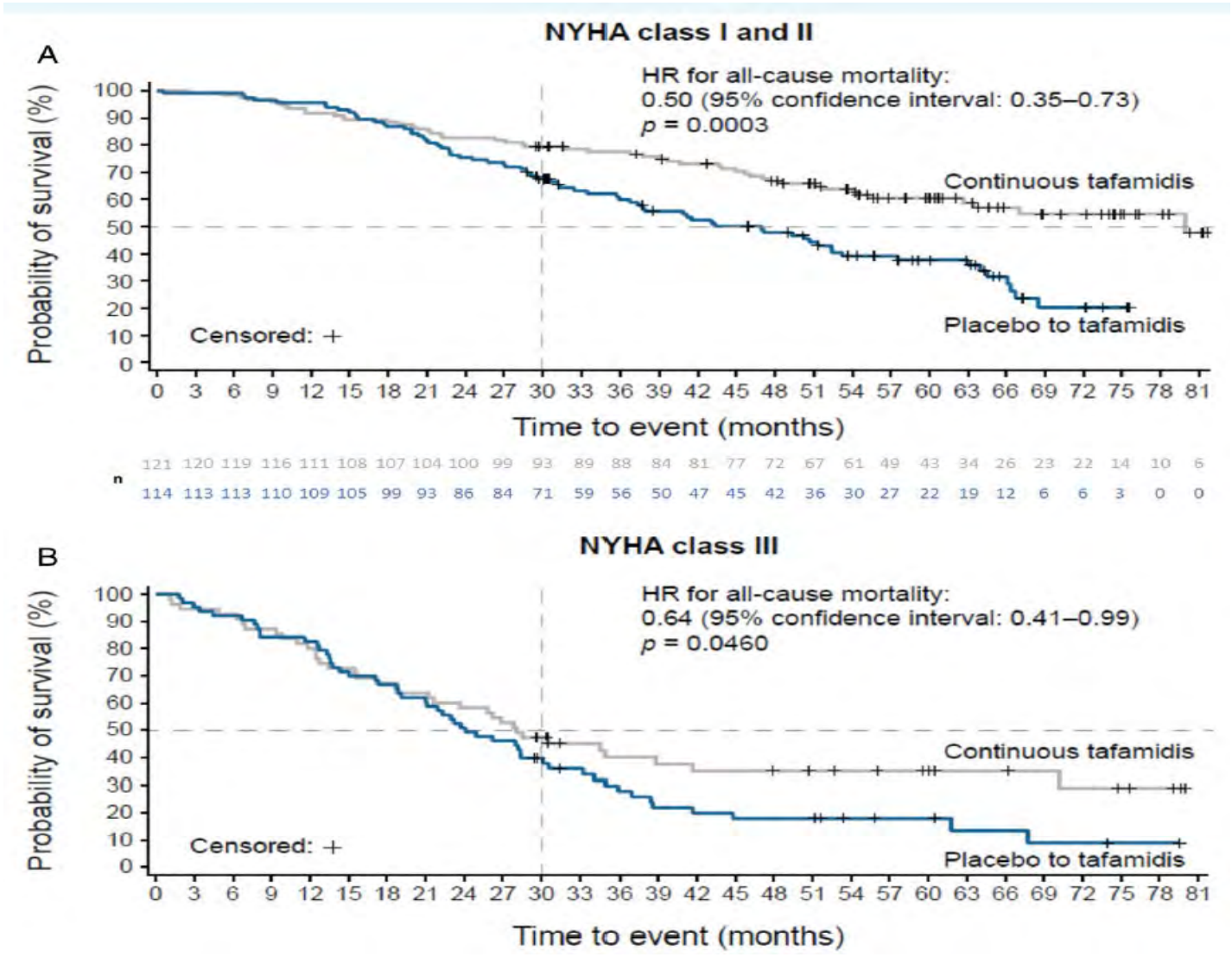
+

Desaconsellem BB especialment si **incompetència cronotròpica** (estudi PRESERVE-HR):



Quadríptic ICFEP SEMI
Palau P. J Am Coll Cardiol 2021;78:2042–2056

Etiologia específica: amiloïdosi aTTR



Pacients amb IC I amiloïdosi aTTR confirmada; **FEVE mitjana 48%**

Efecte significatiu en **mortalitat a llarg termini** amb **tafamidis** (50% NYHA I-II. 32% NYHA III)

El benefici triga a aparèixer (15-18 mesos) però es manté **més enllà de 6 anys**

Elliott European Journal of Heart Failure (2023) 25, 2060–2064

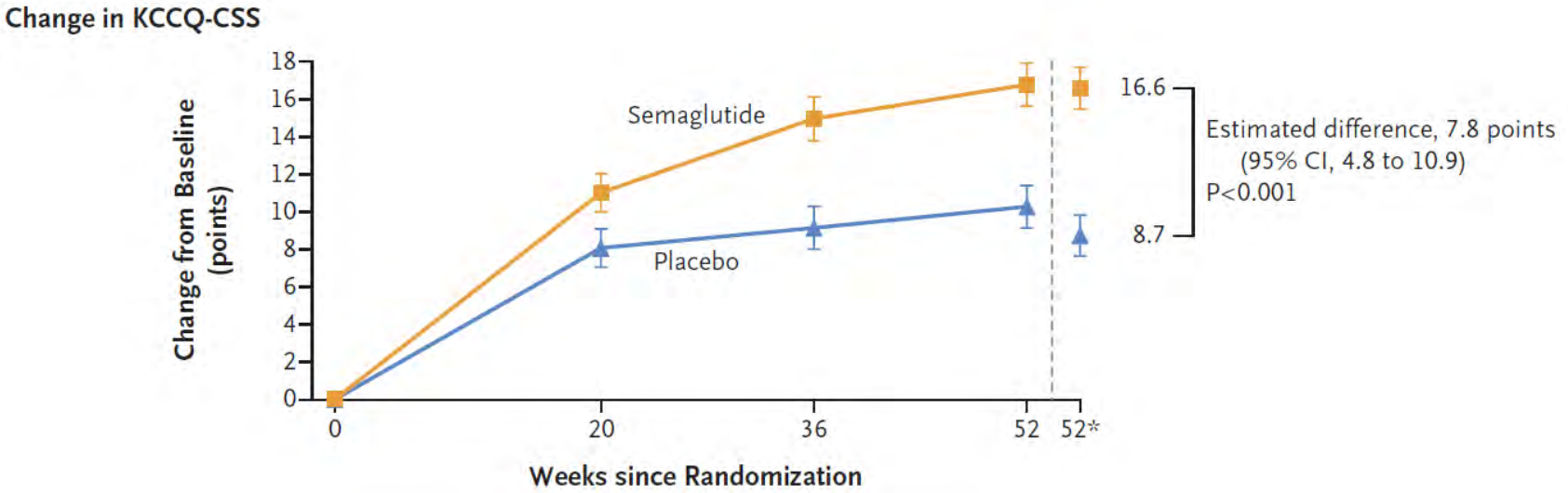
Etiologia “específica”: obesitat

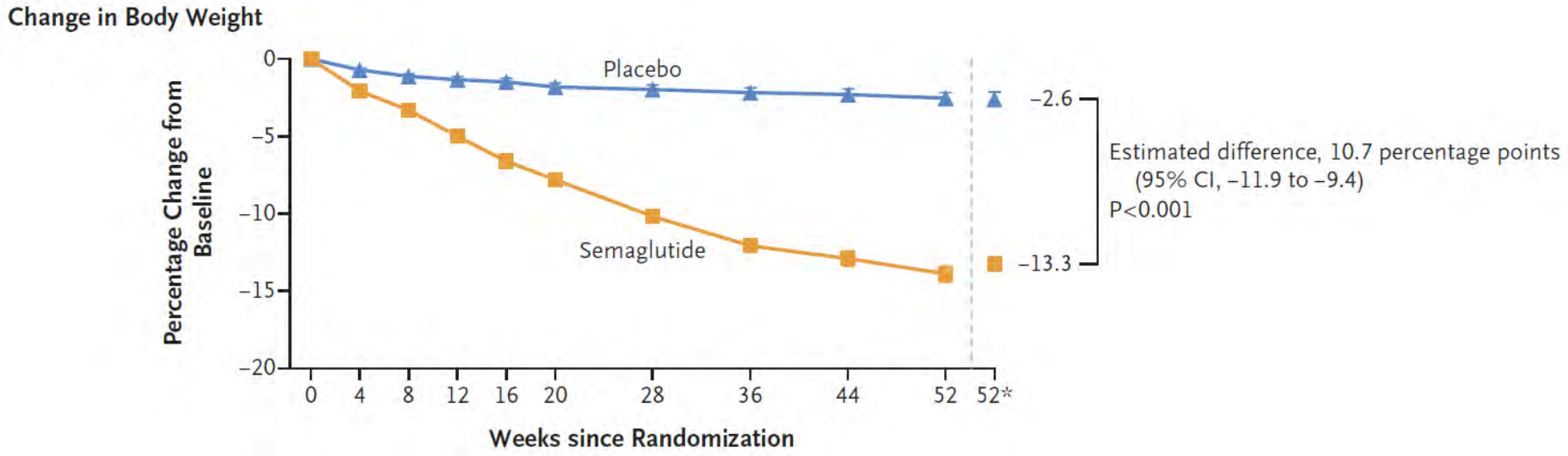
STEP-HFpEF

Pacients amb IC i **FEVE > 45%** + **IMC > 30** + pobra qualitat de vida (**KCCQ-CSS < 90**), no DM!

Efecte significatiu en **pèrdua de pes i millora QV** (*end-points* principals) amb **semaglutide (aGLP-1)**

End-point jeràrquic (**mort + agudització IC + canvis KCCQ i 6-MWT**): anàlisi *win-ratio* guanyat per semaglutide (WR 1.72; 95% IC 1.37 - 2.15; P<0.001)... a expenses dels dos *end-points* principals





Kosiborod MN. N Engl J Med 2023;389:1069-84

I si la FEVE és intermèdia? Segueix servint tot això?

Indicacions IIb

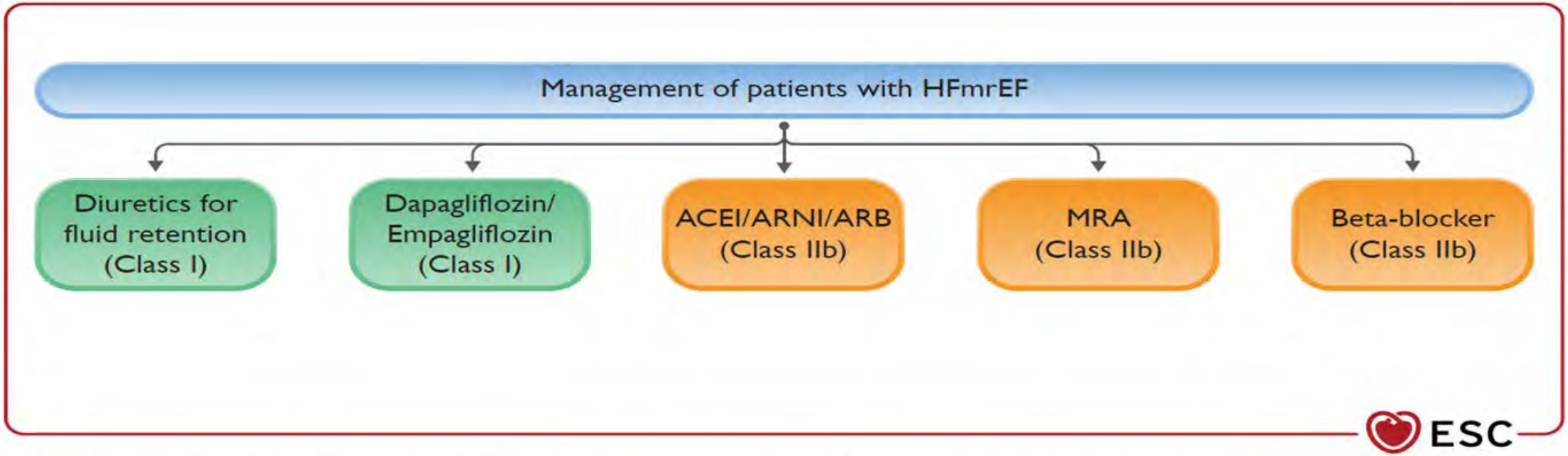
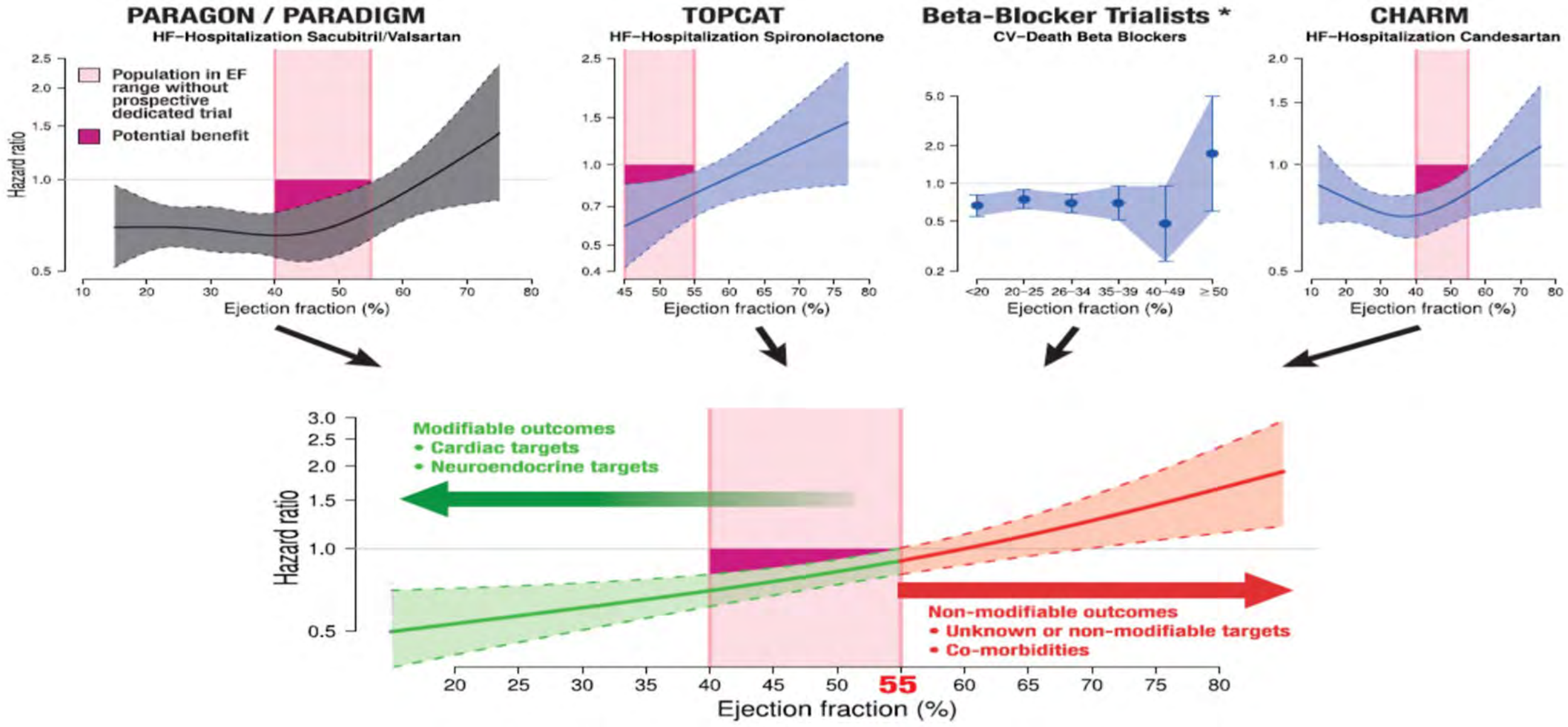
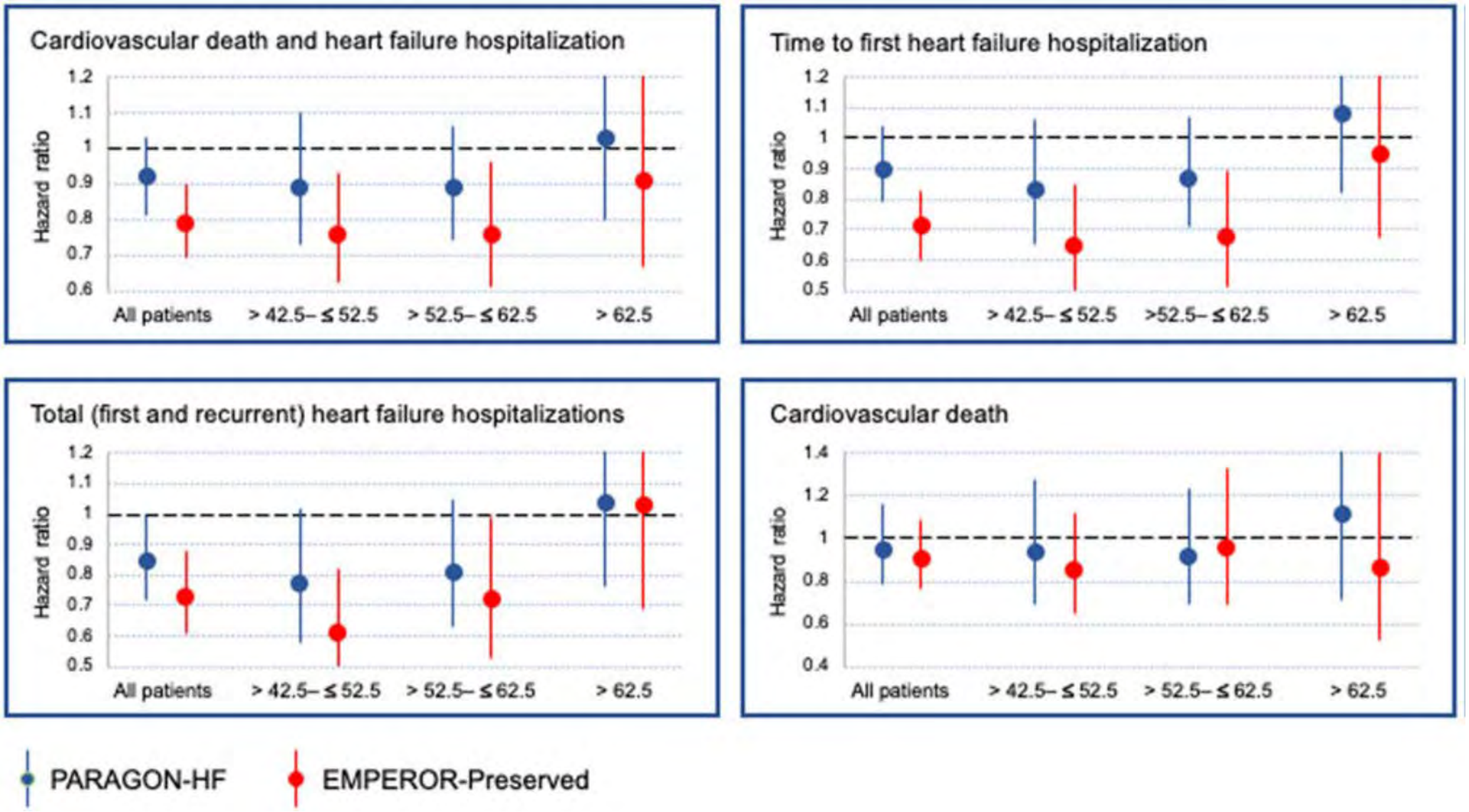


Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

PARAGON + exploració post-hoc estudis ICFEP



Avaluació directa ICFEmr-p: ARNI i iSGLT2



Packer M. Circulation. 2021;144:1193–1195

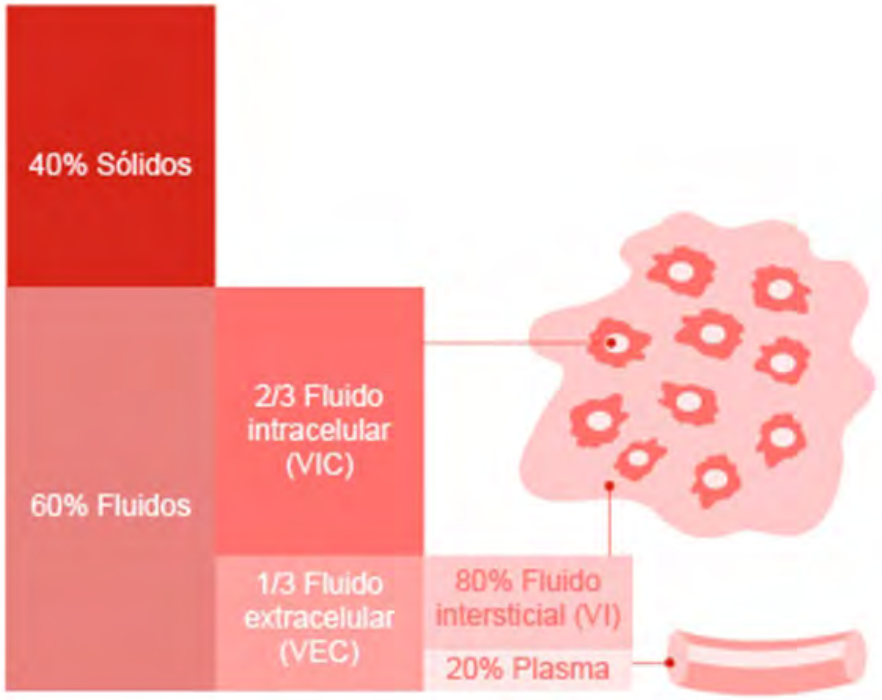
Criteris inclusió i exclusió assajos ICFEP

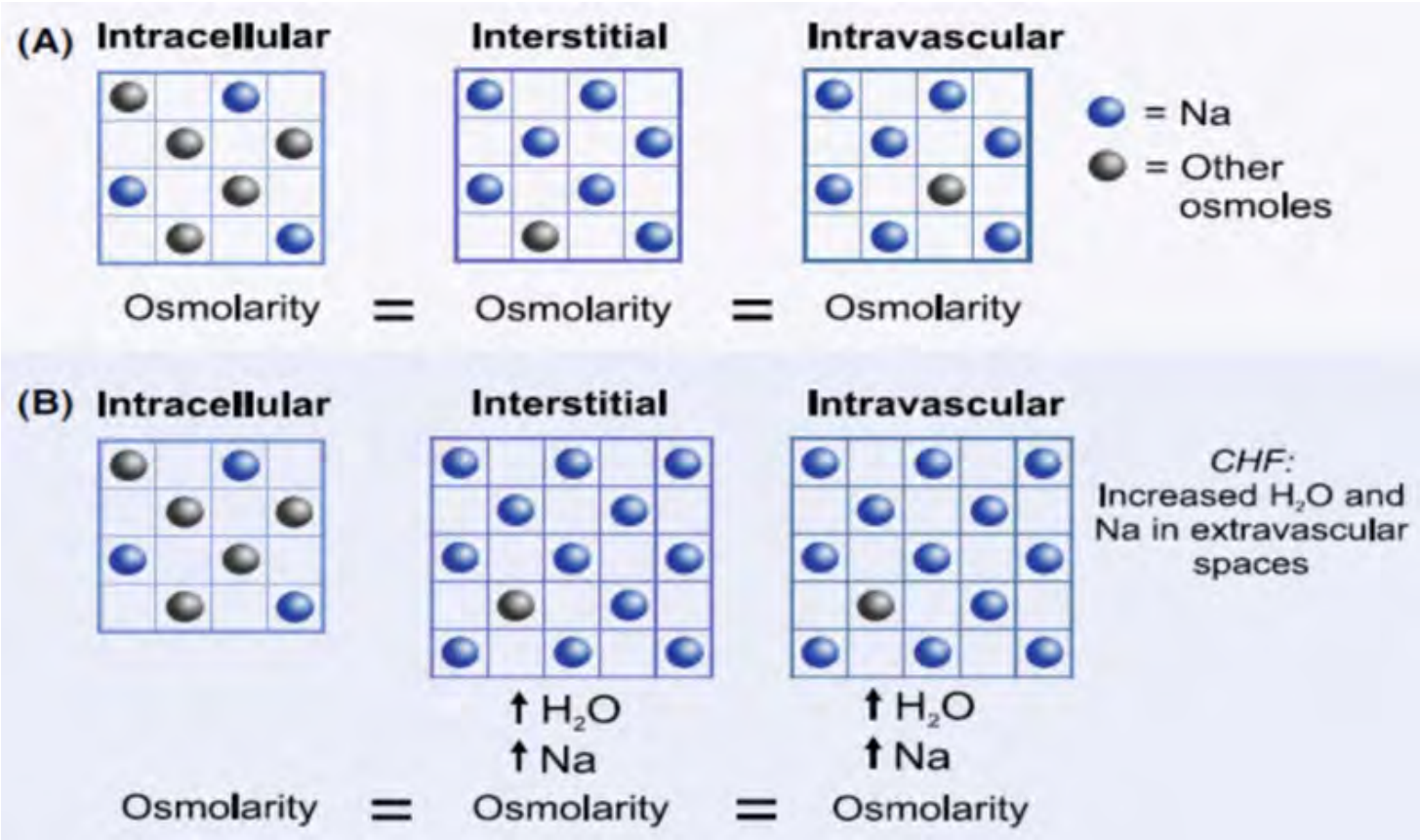
ESTUDIO	FEVI MINIMA	% FA	PEPTIDOS	PARAMETROS VI	PARAMETROS AI	FUNCION RENAL	EXCLUSION
DELIVER	40	56	SI	Hipertrofia septo o pared posterior	Indices diámetro y volumen	eFG > 25	Infiltrativa/hipertrofia/constrictiva/genética HTP primaria Valvulopatia no corregida
EMPEROR-p	40	52	SI	Hipertrofia septo; masa VI; E/e´o e'	Indices diámetro y volumen	eFG > 25	Infiltrativa/hipertrofia/constrictiva/genética HTP primaria Valvulopatia no corregida FA > 110x'
PARAGON	45	33	SI	Hipertrofia septo	Indices diámetro y volumen	eFG > 25	Infiltrativa/hipertrofia/constrictiva/genética HTP primaria Valvulopatia no corregida ICD sin clínica previa ICI
TOPCAT	45	36	SI o ingreso previo x IC	-	-	eFG > 25 o Cr < 2,5 mg/dL	Infiltrativa/hipertrofia/constrictiva/genética Valvulopatia no corregida FA > 90x'
CHARM-p	40	29	-	-	-	Cr < 3 mg/dL	
PEP-CHF	40	20	-	Hipertrofia septo; E/A; TD, TRIV	Indice volumen	Cr < 200 mmol/L	
I-PRESERVE	45	29	-	Hipertrofia VI (ECG o ECO) o BRI (ECG)	Diámetro	Cr < 2,5 mg/dL	Cor pulmonale
J-DHF	40	27	-	-	-	eFG > 30 o Cr < 3,0 mg/dL	Obstructiva HTP primaria IAo o IM "relevantes"
DIG-PEF	45	No	-	-	-	Cr < 3 mg/dL	Cor pulmonale

Ara el tinc “descompensat” a Urgències. Quin és el millor tractament?

Què és la congestió?

Acumulació de líquid als compartiments **intravascular i extravascular** a conseqüència de **l'augment** de les **pressions d'ompliment cardíaques**



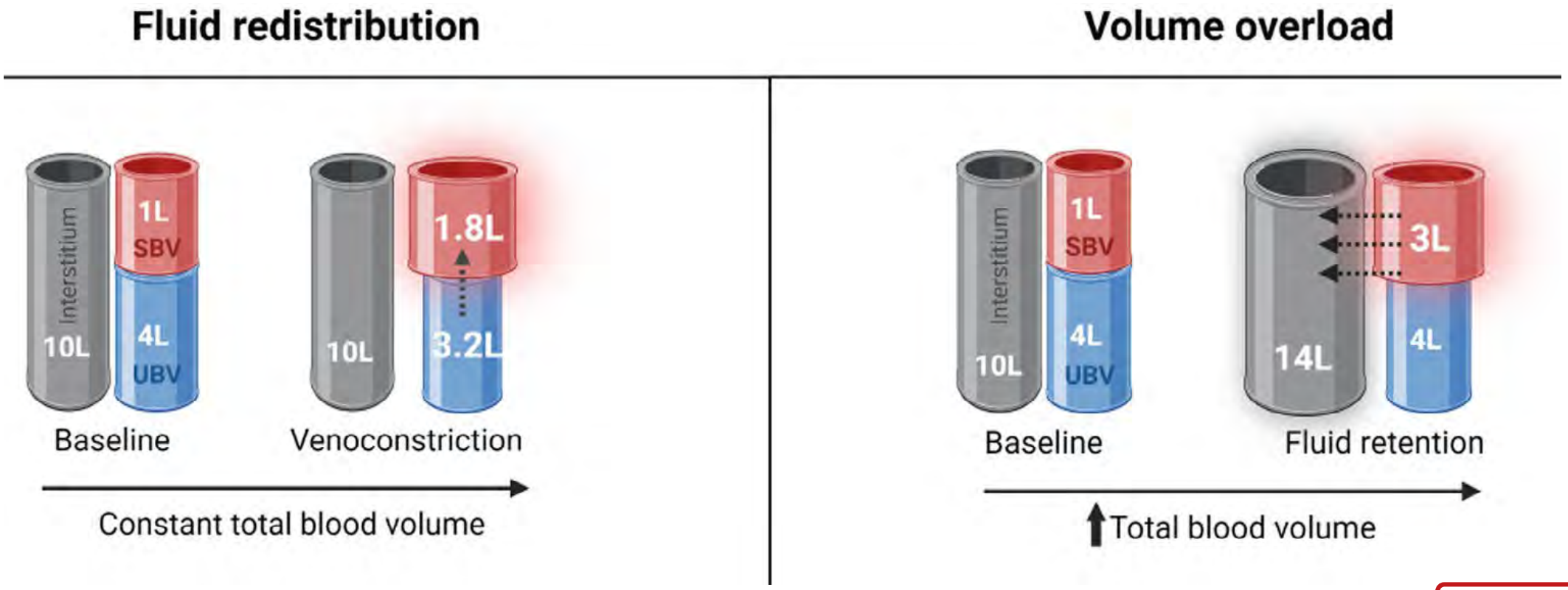


Oyama J Vet Intern Med 2023

Congestió ≠ sobrecàrrega de volum

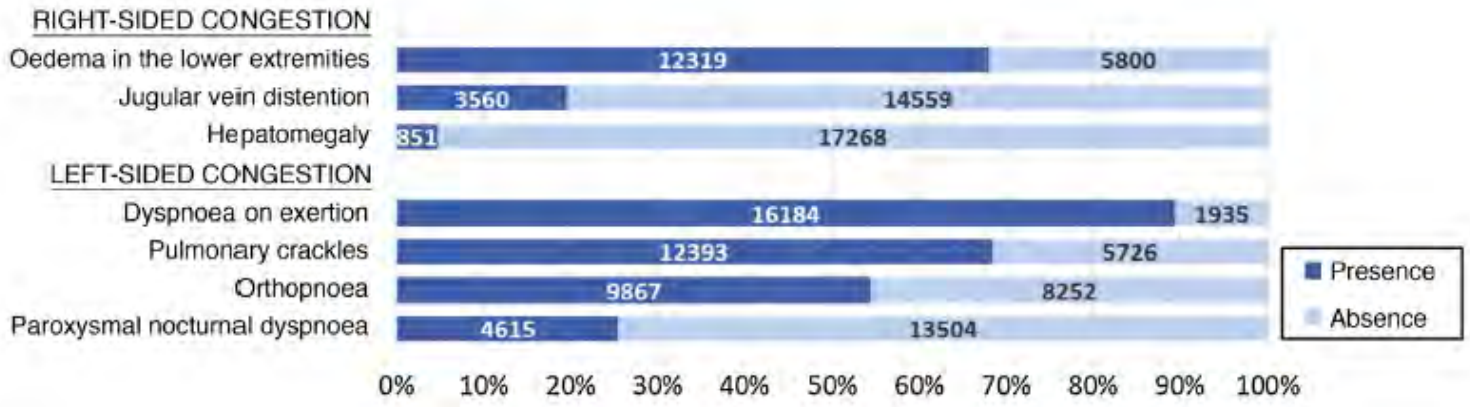
A mateix volum sanguini, la **redistribució** de líquid des del **compartiment venós** a l'arterial actua com una "sobrecàrrega de volum endògena"

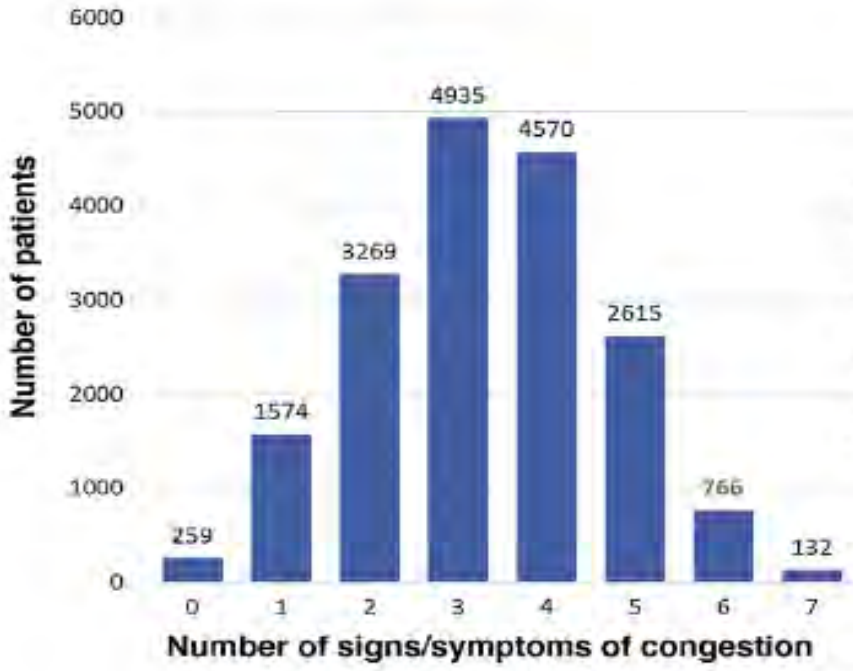
La sobrecàrrega real es deu a la **retenció hidrosalina**

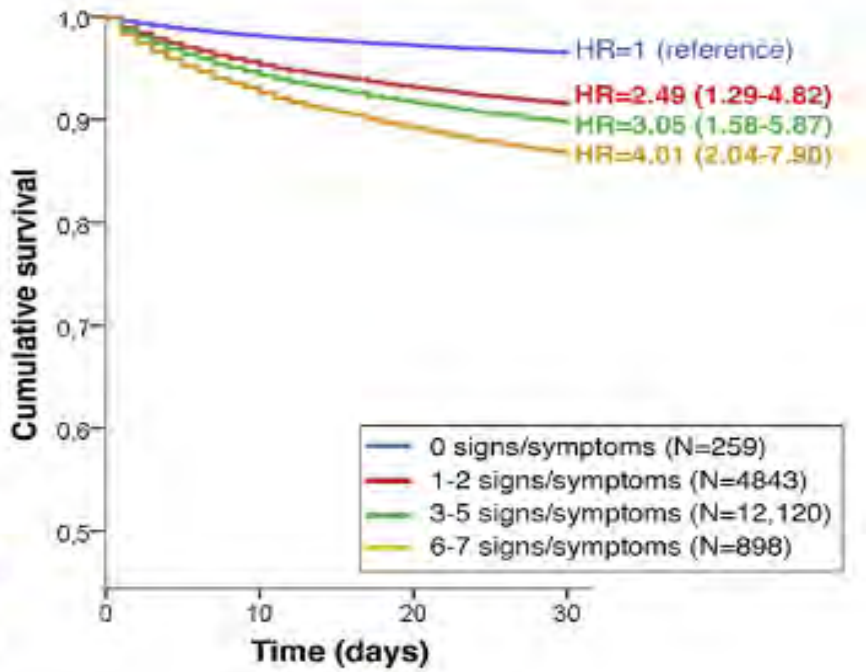


Núñez Eur J Heart Fail 2022

Congestió a l'ingrés = risc







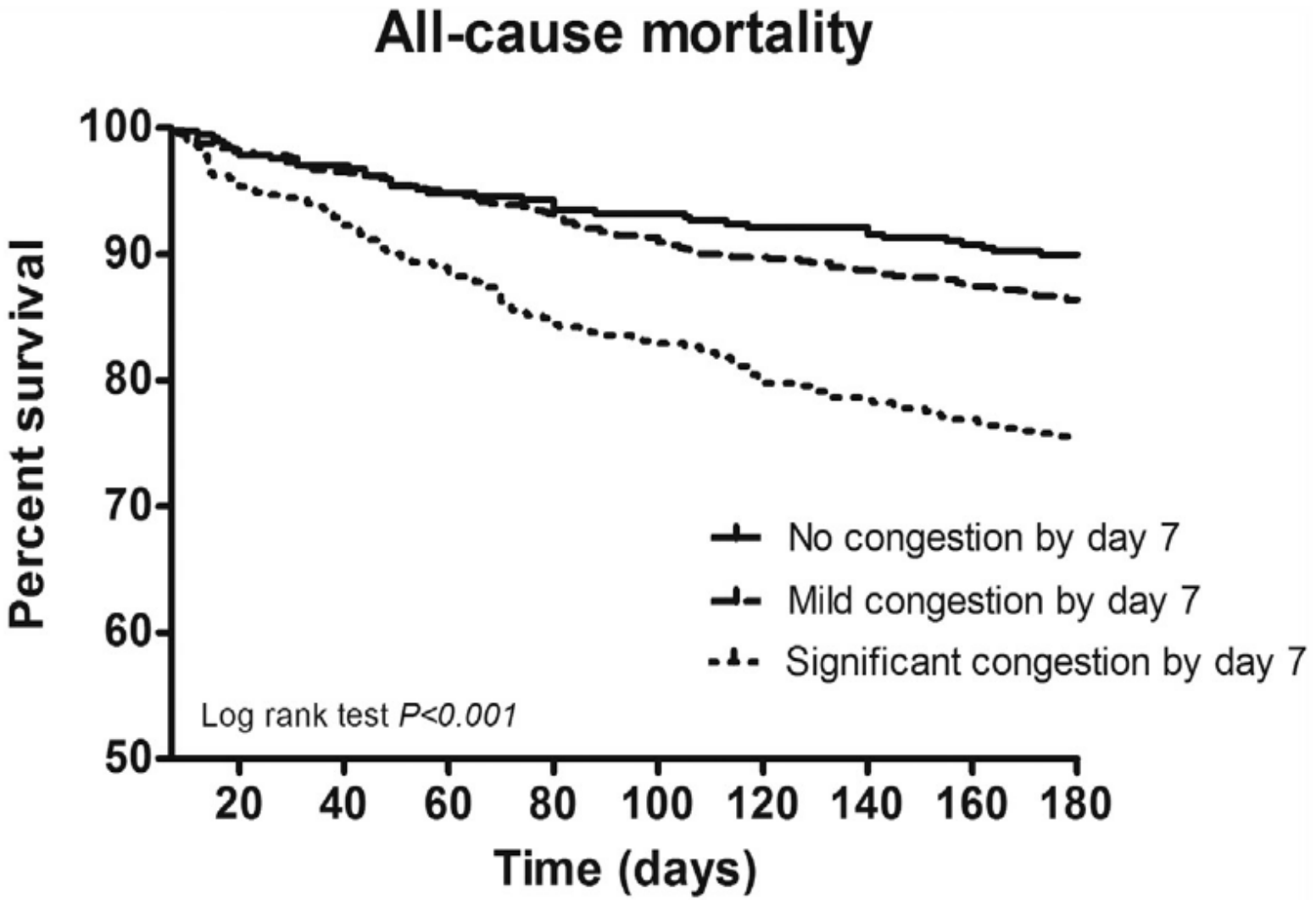
La majoria dels pacients del registre ICA-SEMES tenen **≥ 2 símptomes/signes** congestius a Urgències

A major nombre major risc de **mortalitat a curt termini**

Espinosa Rev Clin Esp 2022

Congestió no resolta = risc

Risc significatiu de **mortalitat** en pacients amb ICA altats que tenien **congestió residual significativa** al 7è dia d'ingrés



Rubio-Gracia Int J Cardiol 2018

Valor de l'exploració física en congestió

Table 3. Utility of Components of the H&P Examination in Detecting PCWP >22 mm Hg

				Predictive Value		LR		
H&P Finding	Frequency	Sensitivity	Specificity	Positive	Negative	Positive	Negative	OR (95% CI)
Rales (≥1/3 lung fields)	26/192	15	89	69	38	1.32	1.04	1.4 (0.6, 3.4)
S3	123/192	62	32	61	33	0.92	0.85	0.8 (0.4, 1.5)
Ascites (moderate/massive)	31/192	21	92	81	40	2.44	1.15	2.8 (1.1, 7.3)
Edema (≥2+)	73/192	41	66	67	40	1.20	1.11	1.3 (0.7, 2.5)
Orthopnea (≥2 pillows)	157/192	86	25	66	51	1.15	1.80	2.1 (1, 4.4)
Hepatomegaly (>4 finger breadths)	23/191	15	93	78	39	2.13	1.09	2.3 (0.8, 6.6)
Hepatojugular reflux	147/186	83	27	65	49	1.13	1.54	1.7 (0.9, 3.5)
JVP ≥12 mm Hg	101/186	65	64	75	52	1.79	1.82	3.3 (1.8, 6.1)
JVP <8 mm Hg	18/186	4.3	81	28	33	0.23	0.85	0.2 (0.07, 0.6)

Values expressed as percentages unless otherwise indicated. LR indicates likelihood ratio; OR, odds ratio.

En la IC avançada, **el ↑ de la pressió venosa jugular (la IJ)** és la dada que millor correlaciona amb una **PCWP elevada** (i si és no hi ha IJ/RHJ la OR de congestió és molt baixa)

Els símptomes són en general poc específics; el millor de tots **l'ortopnea**

Thibodeau JACC Heart Fail 2018

Table 1 | Commonly used congestion scores in trials on acute heart failure

Sign or symptom	Points	EVEREST[135] and EMPA-RESPONSE-AHF[136]	OPTIMIZE-HF[137]	Composite congestion score (EVEREST)[135]	ASCEND-HF[138]	Composite congestion score (PROTECT)[5,72]	Orthoedema score (CARRESS-HF and DOSE-HF)[139]
Peripheral oedema	0	Absent or trace	Absent	Absent	Absent	Absent	Trace
	1	Slight	1+	Slight	Up to shins	Slight	Moderate
	2	Moderate	2+	Moderate	Up to knees	Moderate	Severe
	3	Marked	3+	Marked	Up to sacrum	Marked	–
Orthopnoea	0	None	No	None	No	None	<2 pillows
	1	Seldom	–	2 pillows	–	2 pillows	–
	2	Frequent	Yes	3 pillows	Yes	3 pillows	≥2 pillows
	3	Continuous	–	>30°	–	>30°	–
Dyspnoea	0	None	No	Not included	Not included	Not included	Not included
	1	Seldom	–				
	2	Frequent	On exertion				
	3	Continuous	At rest				
Jugular vein distension (cmH_2O)	0	<6	<6	<6	Not included	<6	Not included
	1	6–9	6–9	6–9		6–10	
	2	10–15	10–15	10–15		>10	
	3	>15	>15	>15		–	
Rales	0	None	None	Not included	Not included	Not included	Not included
	1	Basal	<1/3				
	2	To <50%	>1/3				
	3	To >50%	–				
Fatigue	0	None	No	Not included	Not included	Not included	Not included
	1	Seldom	–				
	2	Frequent	Yes				
	3	Continuous	–				
Plasma NT-proBNP level	1	Not included	Not included	Not included	Tertile 1	Not included	Not included
	2				Tertile 2		
	3				Tertile 3		
Maximum score	–	18	15	9	8	8	4

Scores de congestió

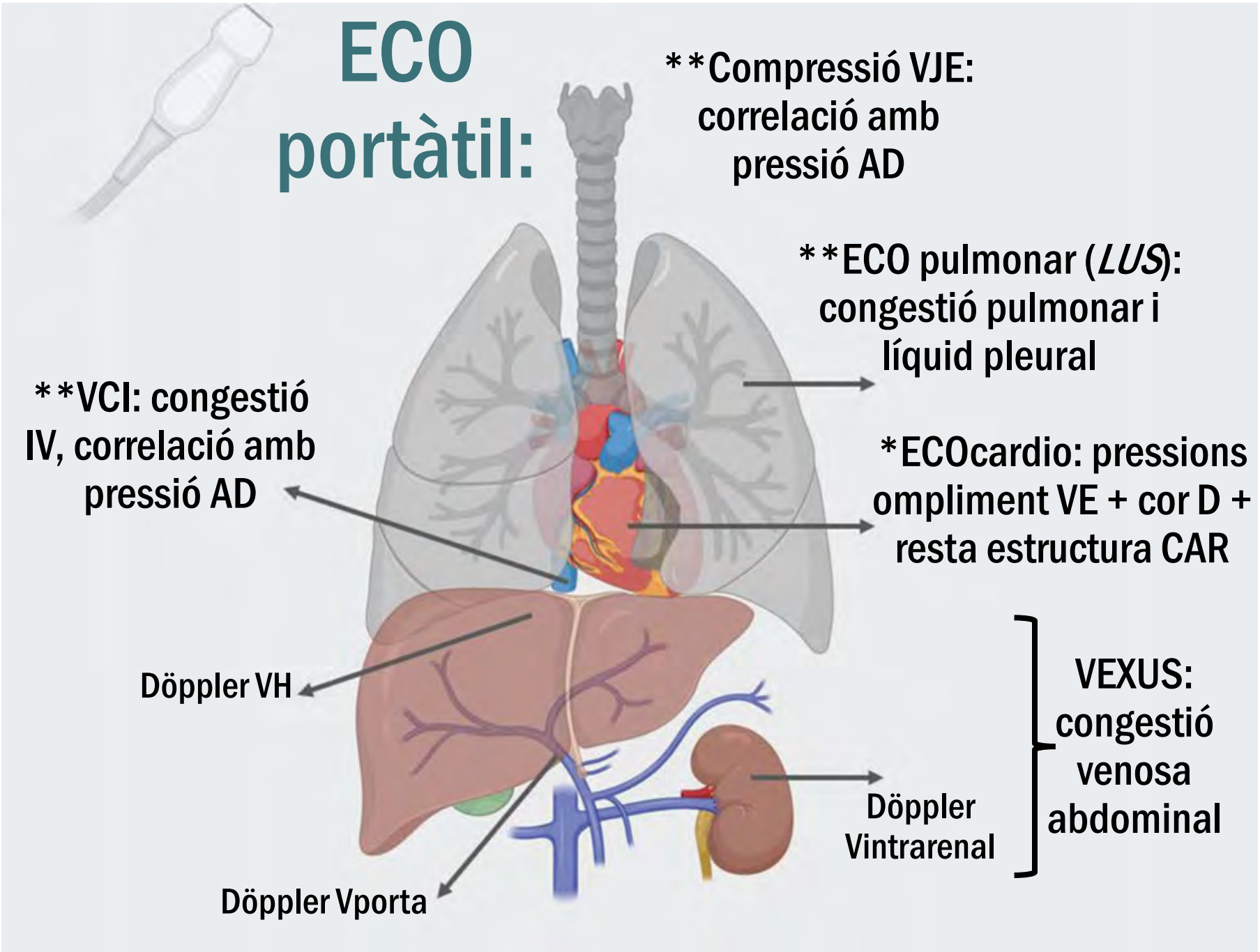
Desenvolupats per a **assajos clínics** de decongestió majoritàriament

Basats en dades sobre tot **clíniques.** Cap incorpora ECO, pocs PN

No validats per guiar tractaments

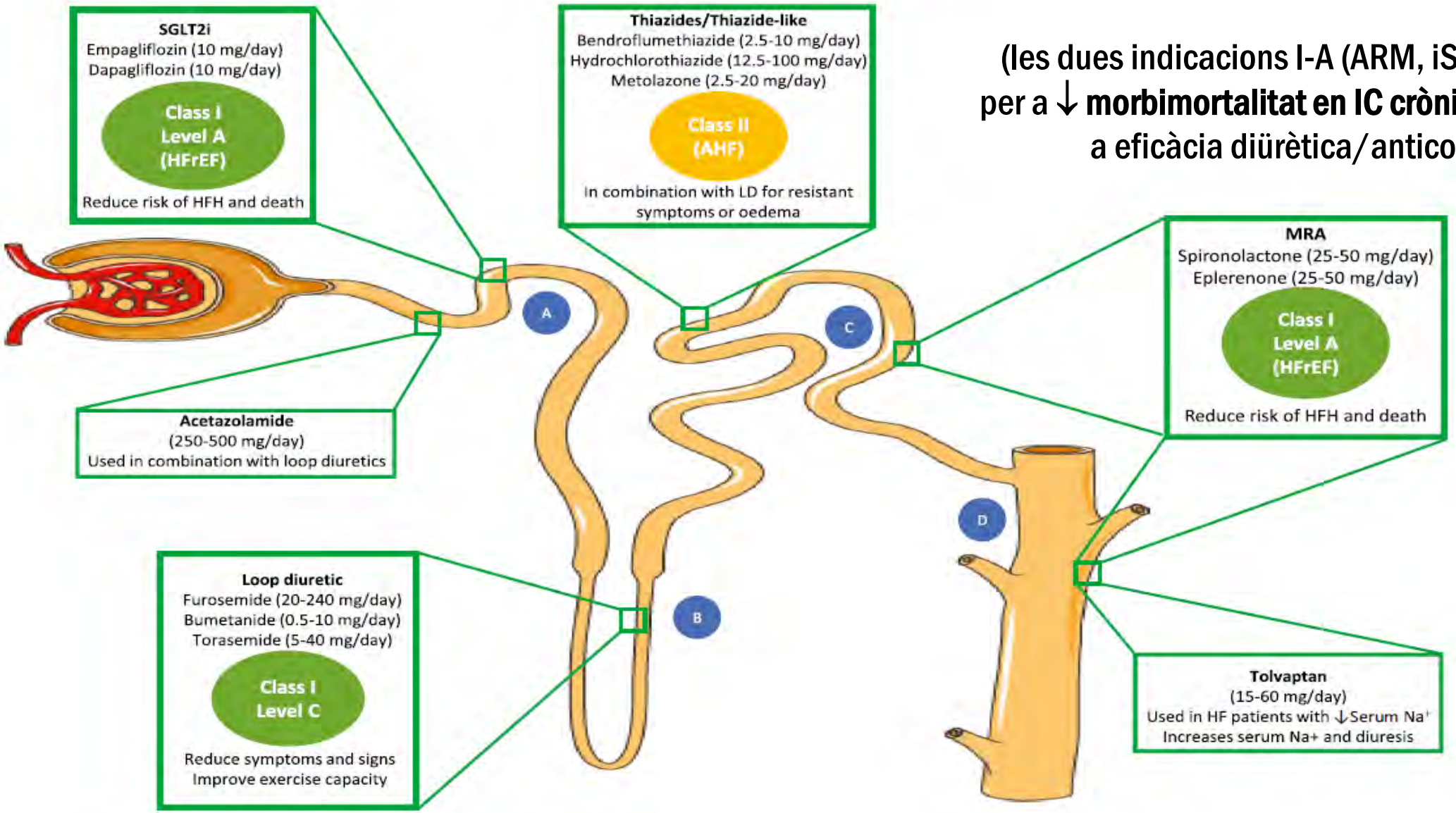
Arrigo Nat Rev Dis Primers 2020

ECO portàtil:



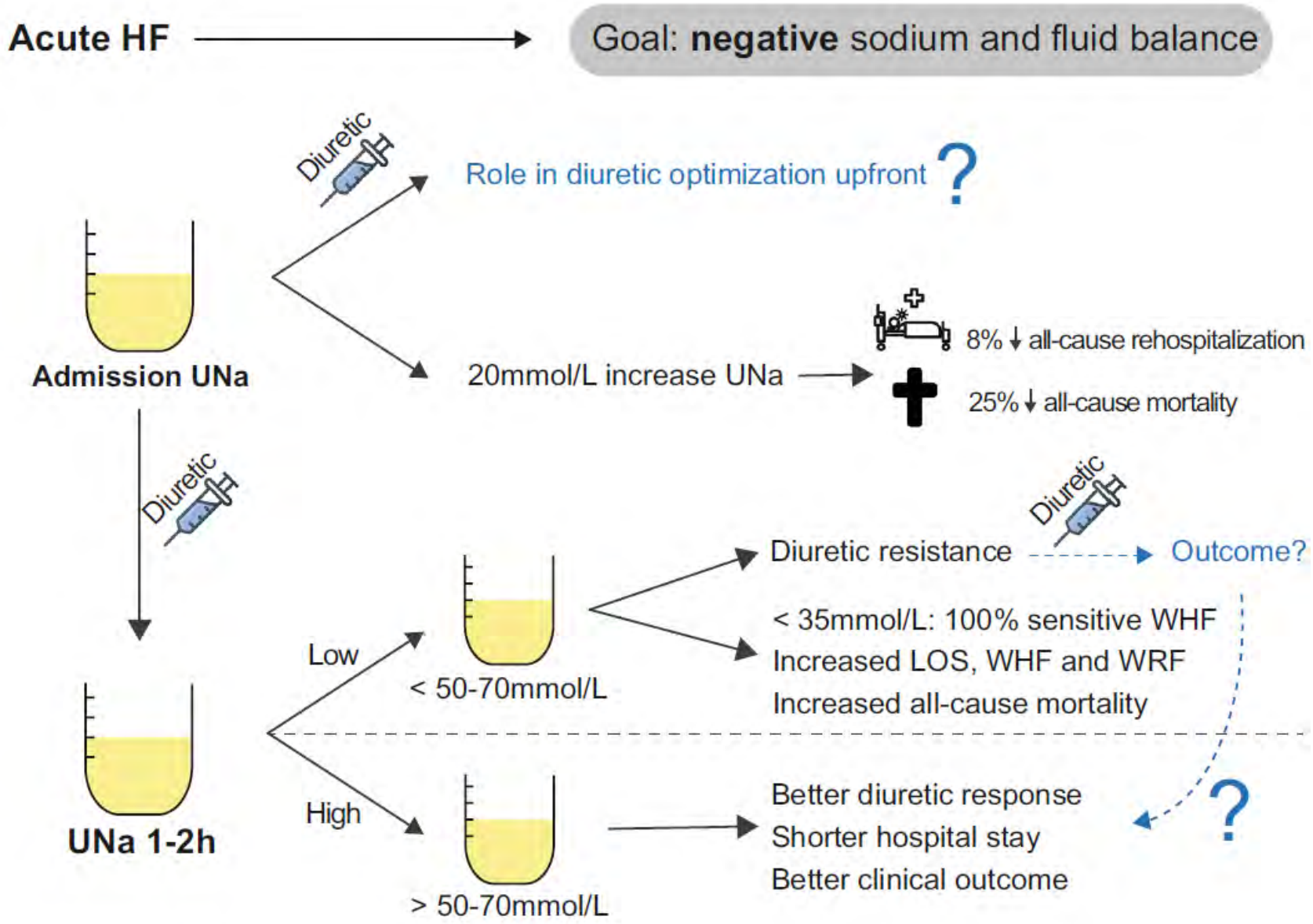
Decongestionem amb la nefrona: diürètics +/- iSGLT2

(les dues indicacions I-A (ARM, iSGLT2) son per a ↓ **morbimortalitat en IC crònica**, no per a eficàcia diürètica/anticongestiva!)



Khan Curr Cardiol Reports 2023

La capacitat per eliminar Na^+, clau de la descongestió



En ICA la bona resposta (= ↑ Na^+ en orina) inicial a una dosi e.v. de F (***diuretic challenge***) prediu menor risc **d'hospitalització i mortalitat**

Un Na^+ en orina **elevat** a les **1-2h** d'inici del tractament amb F s'associa a **bona evolució**

Contràriament, si el Na^+ en orina és **baix** (especialment si **< 35 mmol/L**) els riscos en **morbimortalitat** s'eleven

Recomanacions en ICA

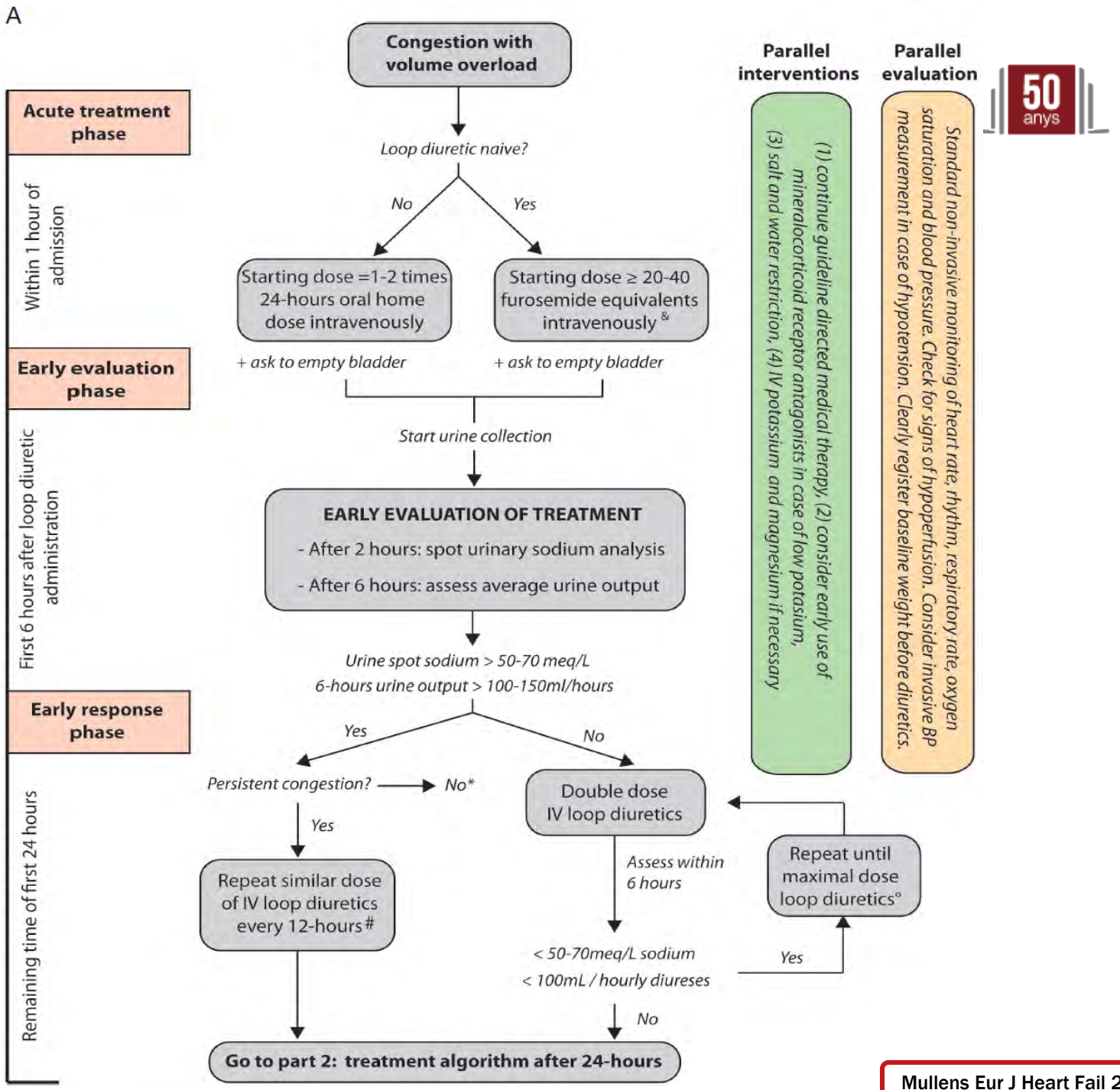
Incorporades a les guies de la ESC 2021

1. Dosi inicial en funció **d'ús previ de F** (aconsellat bolus)

2. Avaluació en funció de la **resposta natriürètica i la diüresi**

3. Increments de dosi fins el **màxim tolerable** (la furosemida té un sostre!)...

4. ...i si no és suficient plantejar teràpia **combinada**



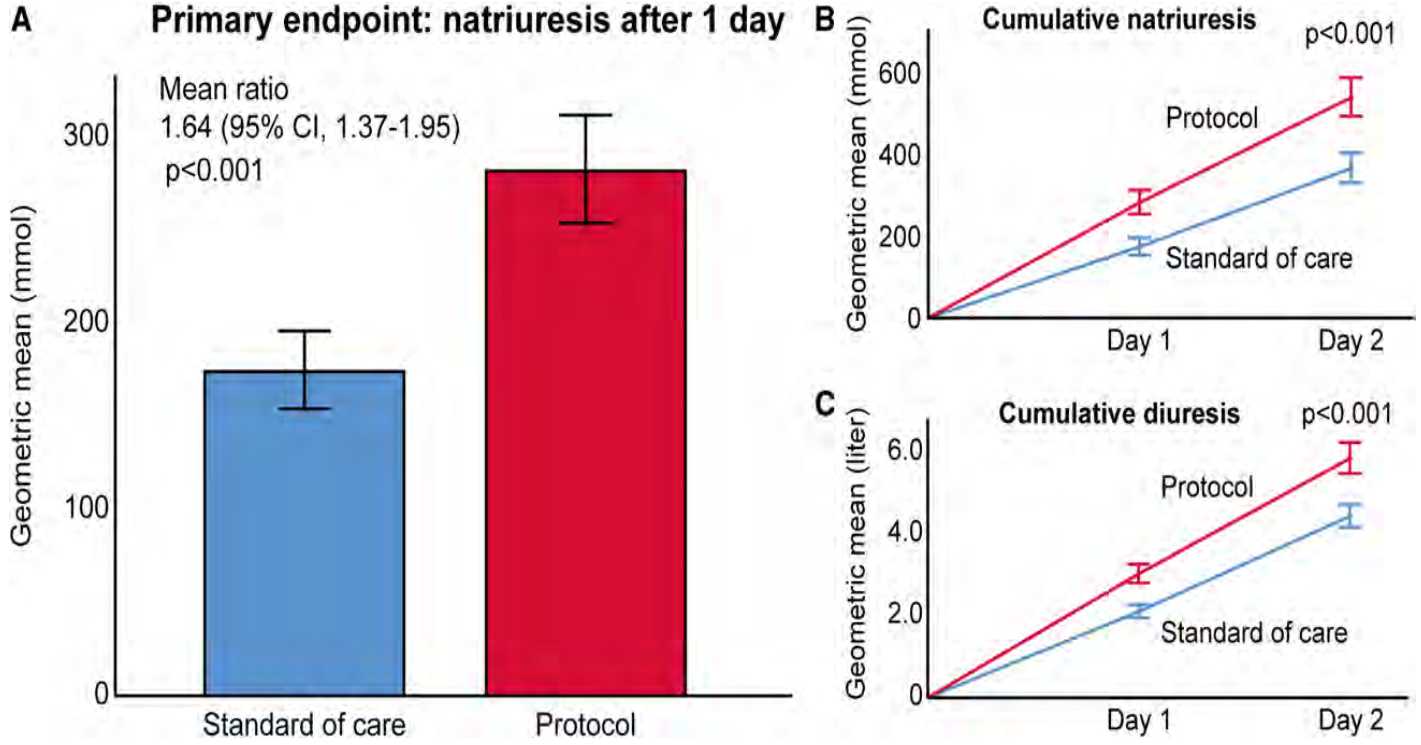
Mullens Eur J Heart Fail 2019

Dos estudis molt recents: PUSH i ENACT-HF

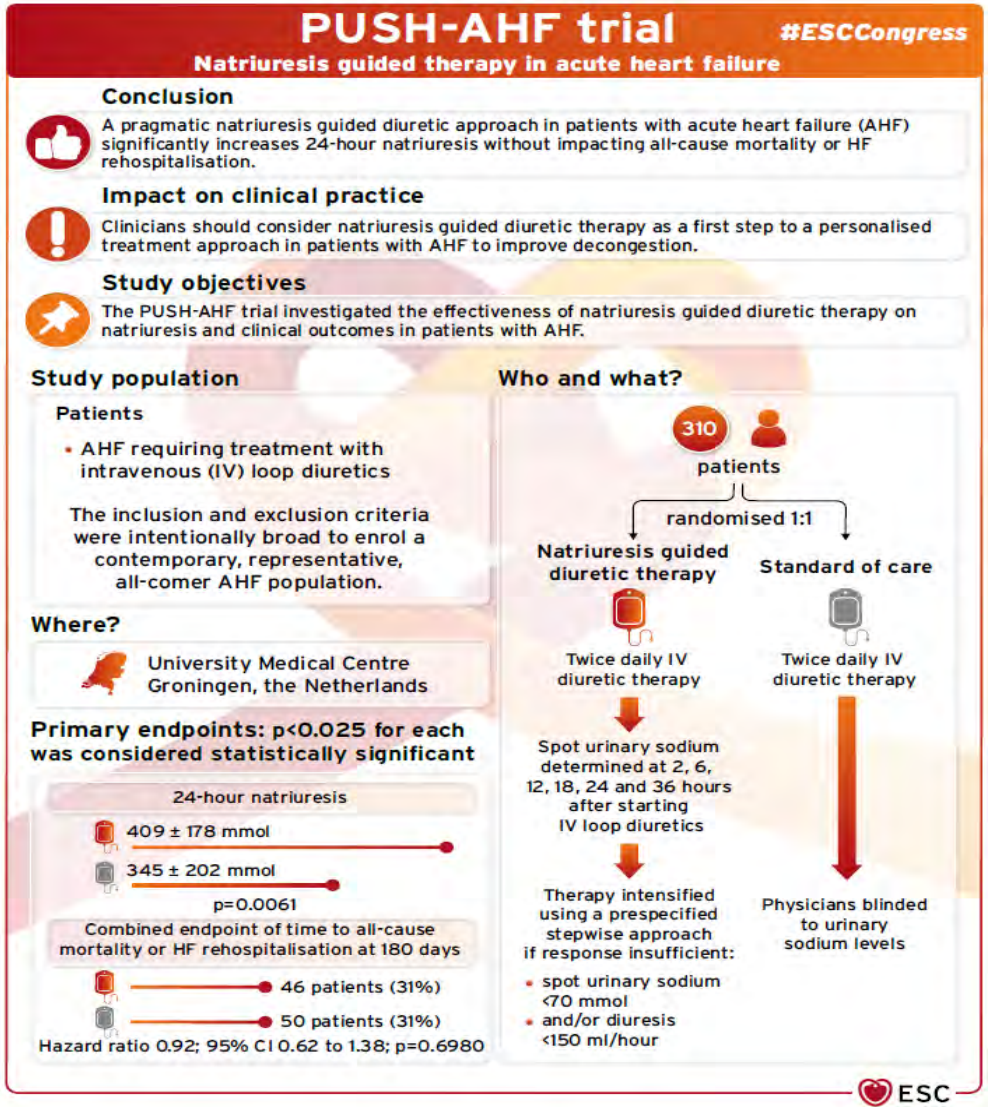
Diüresi guiada per **natriuresi + diüresi** en ICA

Millor resposta natriurètica i diürètica a curt termini intensificant

PUSH-HF no demostra millora en reingrés o mortalitat



Dauw **Circ Heart Fail.** 2024;17:e011105



Ter Maaten ESC Congress 2023

ADVOR: acetazolamida en ICA (I)

ADVOR

Adició d'un IAC (ACZ e.v.) sobre F e.v. en ICA

Predomini **ICFEr-mr, FG 40** ml/min, relativament joves

Dosi prèvia de F v.o. ≈ **40 mg**/dia

Mètrica: **diüresi**, **natriüresi** + avaluació estructurada descongestió (***score*** propi)

EDEMA	No edema (score 0)	Trace edema (pitting disappear immediately) (score 1)	Clear pitting edema (score 2)	Visual deformation above ankle (score 3)	Visual deformation above knee (score 4)
PLEURAL EFFUSION (to be confirmed by chest X-ray or ultrasound on admission if suspected)	No pleural effusion (score 0)	Minor (non-amenable for punction) pleural effusion (score 2)		Major (amenable for punction) pleural effusion (score 3)	
ASCITES (to be confirmed by ultrasound on admission if suspected)	No ascites (score 0)	Minor ascites, only detected by echography (score 2)		Significant ascites (score 3)	

Successful decongestion

Continue IV diuretic therapy

Mullens N Engl J Med 2023

CLOROTIC: HCTZ en ICA (I)

Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

European Heart Journal (2023) **44**, 411–421

Joan Carles Trullàs [1,2]*, José Luis Morales-Rull[3], Jesús Casado[4], Margarita Carrera-Izquierdo[5], Marta Sánchez-Marteles[6], Alicia Conde-Martel[7], Melitón Francisco Dávila-Ramos[8], Pau Llácer[9], Prado Salamanca-Bautista[10], José Pérez-Silvestre[11], Miguel Ángel Plasín[12], José Manuel Cerqueiro[13], Paloma Gil[14], Francesc Formiga [15], Luis Manzano[16], and CLOROTIC trial investigators

Pacients "mon real": ICA de Medicina Interna Espanya:

> 80a, ♀ ≈ ♂ i ICFEP 65%

IC coneguda (qualsevol FE) amb **resistència D = ≥ 80 mg F/dia**

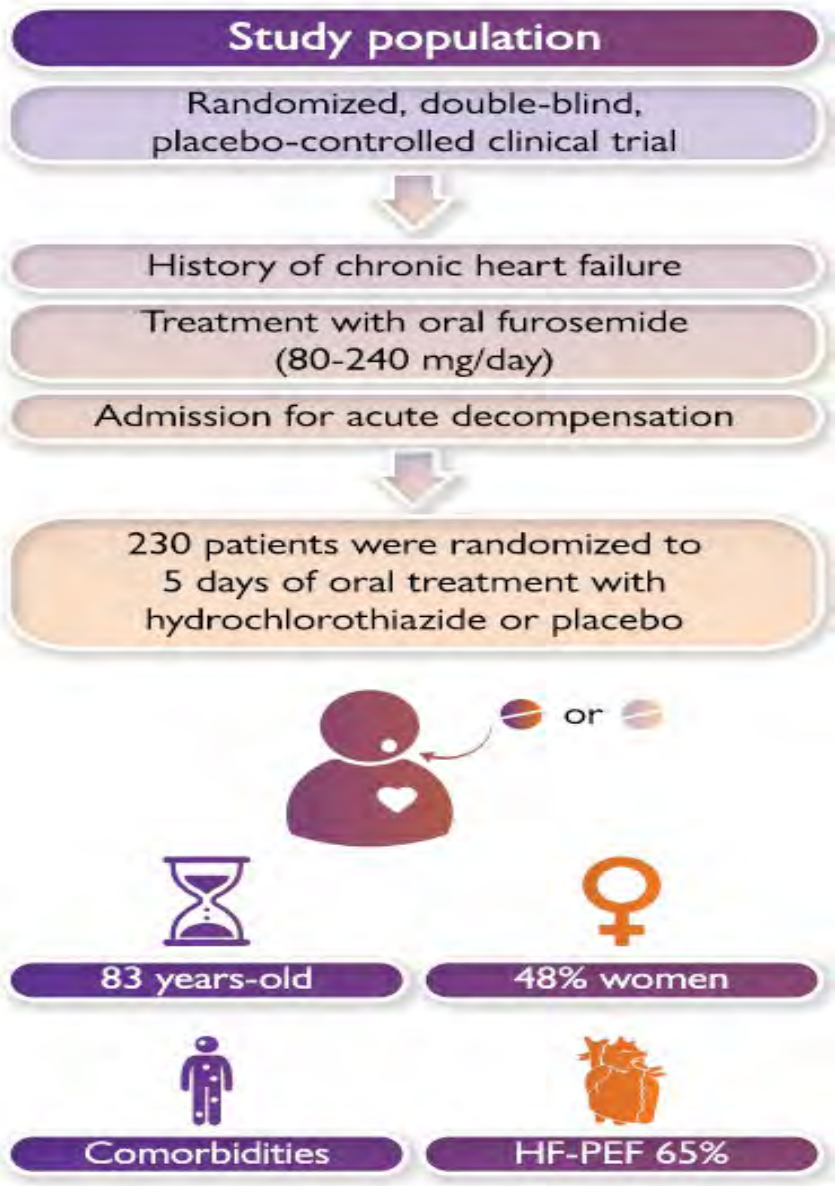
Sense limitacions per FG (15 – 20% IRC grau IV)

F segons protocol + **HCTZ vs placebo oral x 5 dies**

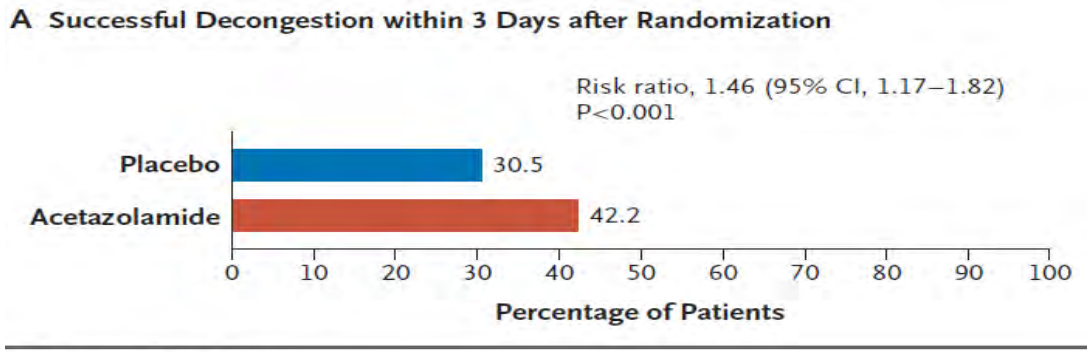
Dosi HCTZ **en funció FG** (25-50-100 mg/dia)

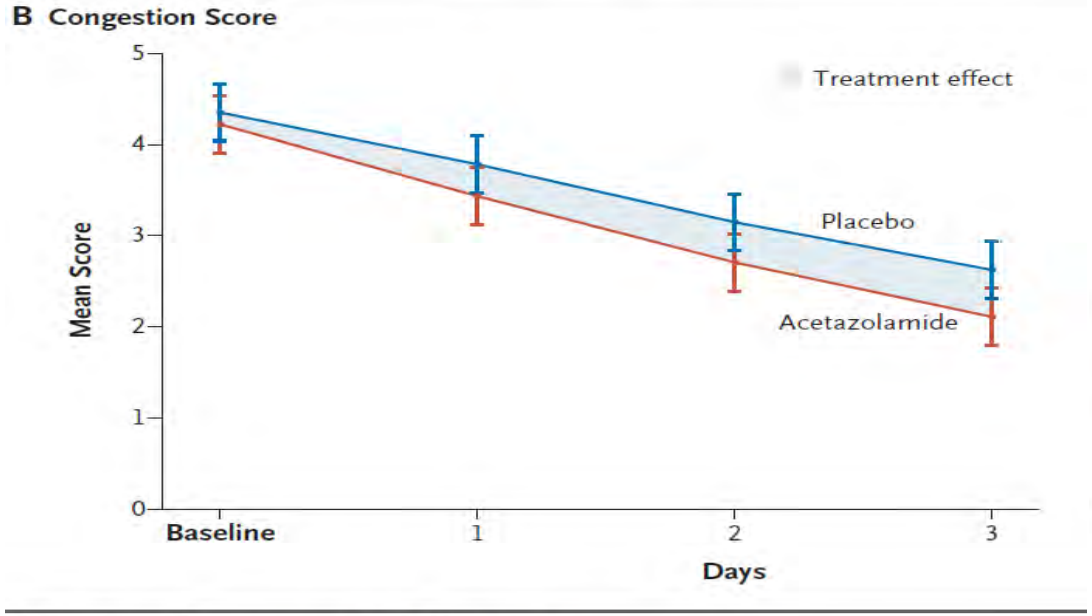
Mètrica descongestió: **pes** (+ resposta clínica a **dispnea**)

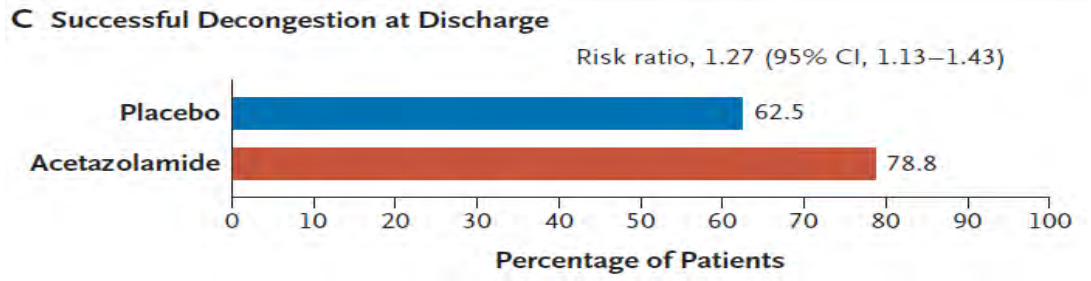
Impacte en FG, ions + morbimortalitat 90d



ADVOR: acetazolamida en ICA (II)

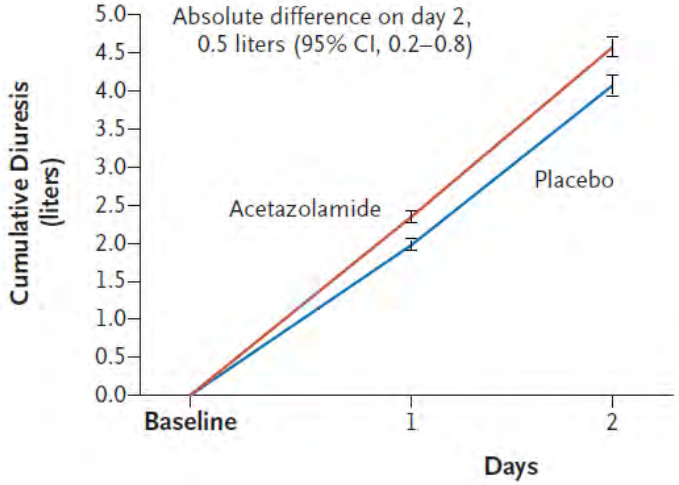


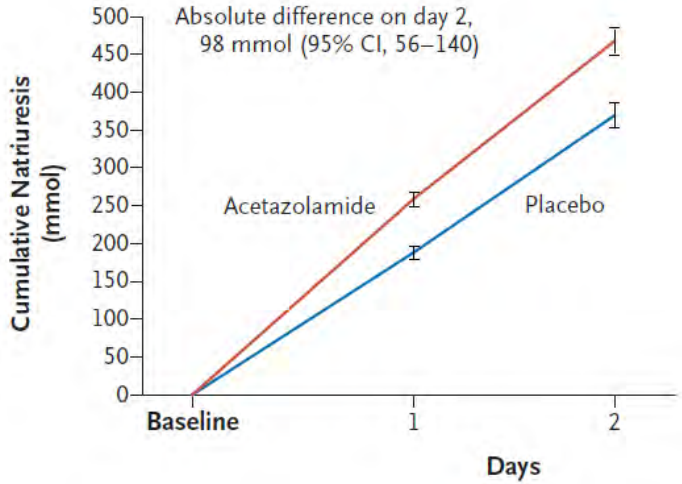




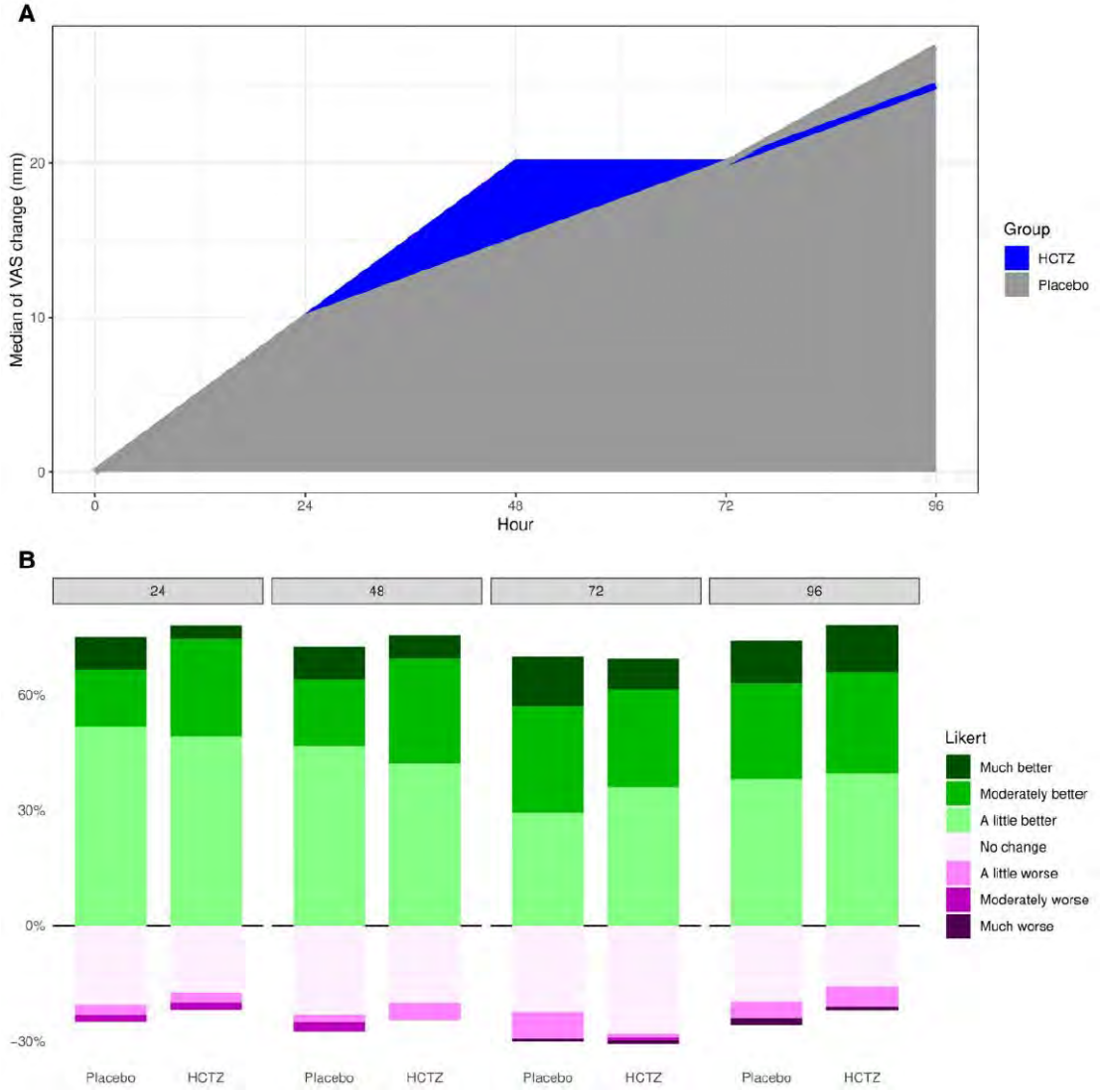
Millora de la **congestió** als 3 dies i l'alta

Millora **diüresi i natriüresi**

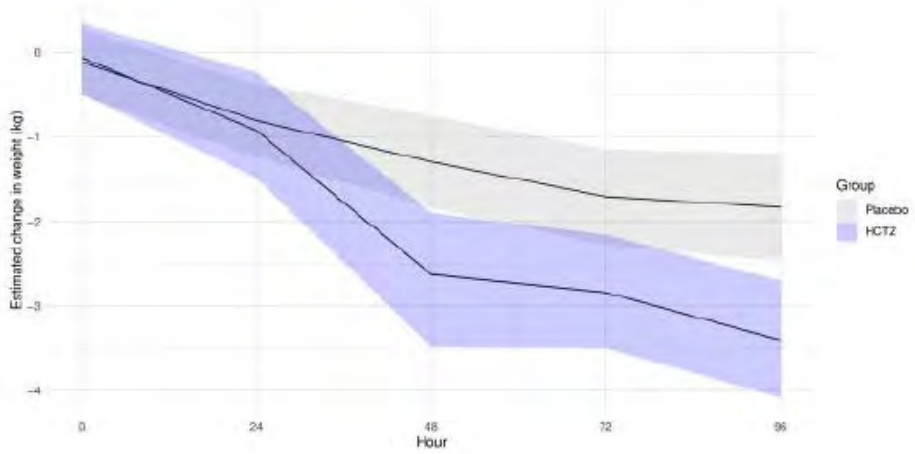




CLOROTIC: HCTZ en ICA (II)



Díspnea similar a 72 i 96h



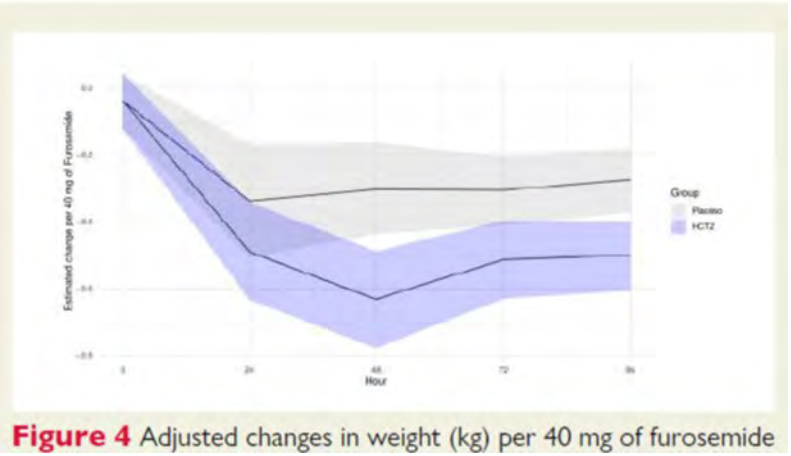
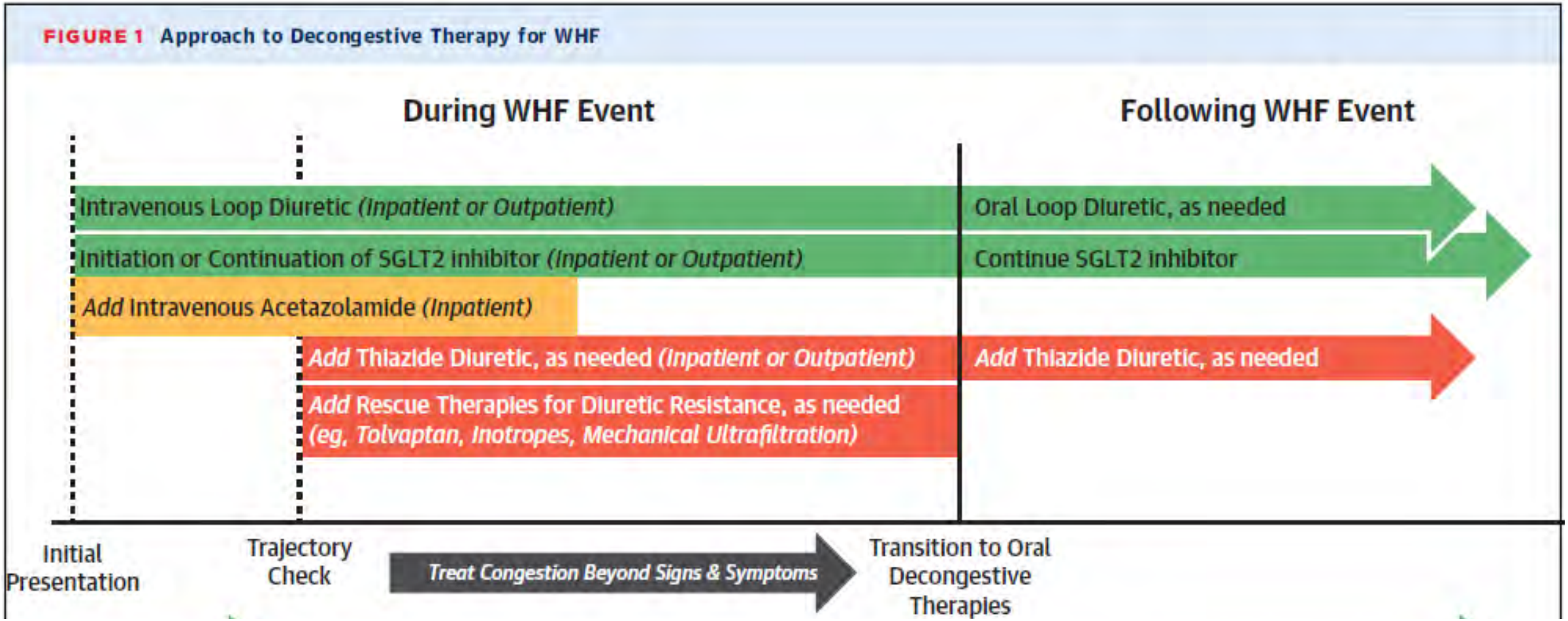


Figure 4 Adjusted changes in weight (kg) per 40 mg of furosemide

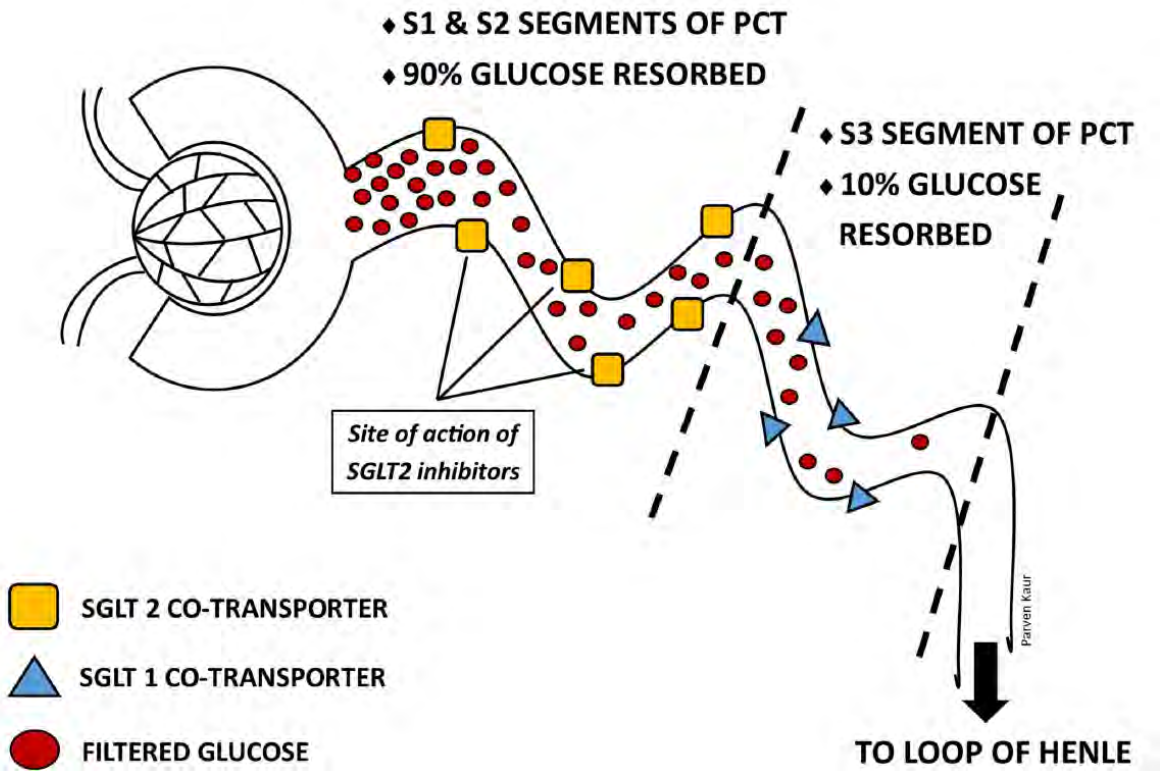
Reducció pes significativa amb HCTZ (global i ajustat per dosi de F prèvia)

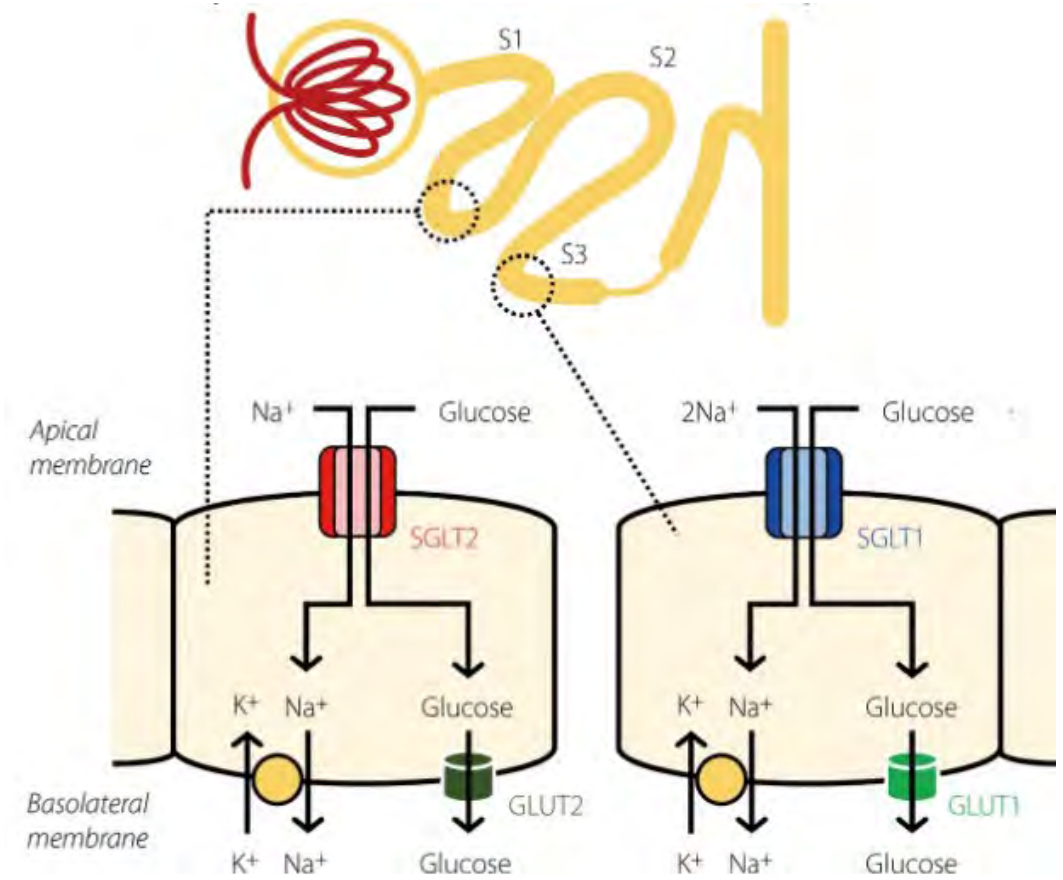
Aproximació a la descongestió



Greene SJ J Am Coll Cardiol 2023;82:559–571

Un nou actor: iSGLT2 com a diürètics





Els iSGLT2 bloquegen el **receptor SGLT2** (cotransportador Na^+ i glucosa) del **túbul proximal**:
La glucosúria genera **diüresi osmòtica**
El bloqueig del receptor també redueix la **reabsorció de Na^+**

Ojha Am J Cardiovasc Drugs 2022
Sano J Diabtis Investig 20202023

Les darreres recomanacions

1	SGLT2-I for all HF patients irrespective of LVEF. Continue SGLT2-I as short-term interruption is associated with ↑ risk for CV-death and HFH If SGLT2-I naive consider initiating SGLT2-I as soon as possible during AHF-episode
2	Optimize loop diuretic dose first (no proven benefit of one type of loop over the other or bolus vs drip) Pick initial dose of loop diuretics based on home dose (*eg x2.5 times*) and baseline eGFR (*higher if low eGFR*) Una guided approach with uptitration of loop diuretic dose if Una<70 mmol/l *(safe and effective approach allowing to overcome underdosing of loop diuretics on individual based needs)*
3	Consider the upfront use of acetazolamide to prevent loop diuretic induced diuretic resistance, improve decongestive response and shorten length of stay if patient was on maintenace loop diuretic at home.
4	If diuretic resistances after loop diuretic optimization (point 2) , add a second agent. Add thiazide if upfront use of acetazolamide. If no upfront use of acetazolamide, make choice between acetazolamide or thiazide. Thiazides might be preferential if chronic high doses of loop diuretics with higher baseline eGFR and no hyponatremia. However close monitoring of potassium is required.
5	Remember other causes contributing to poor diuretic response *If presence of ascites consider a paracentesis (can transduce IAP from Foley if needed)* *Consider presence of low-output state and placement of PAC (consider vasodilators, inotropes or specific devices)* *Consider VExUS score or renal US to determine degree of renal congestion (individualize care approaches)*

Per a tota IC mantenir iSGLT2 o iniciar al més aviat possible

F sempre d'inici, dosis atrevides i (ja es veurà...) guiar per natriüresi

Considerar ACZ d'entrada sempre? A qui no?

Si mala resposta i ja amb ACZ afegir HCTZ

Si no ACZ triar perfil ADVOR (ICFER, poca F basal, FG més baix) o perfil CLOROTIC (ICFEP, més F basal, FG més elevat)

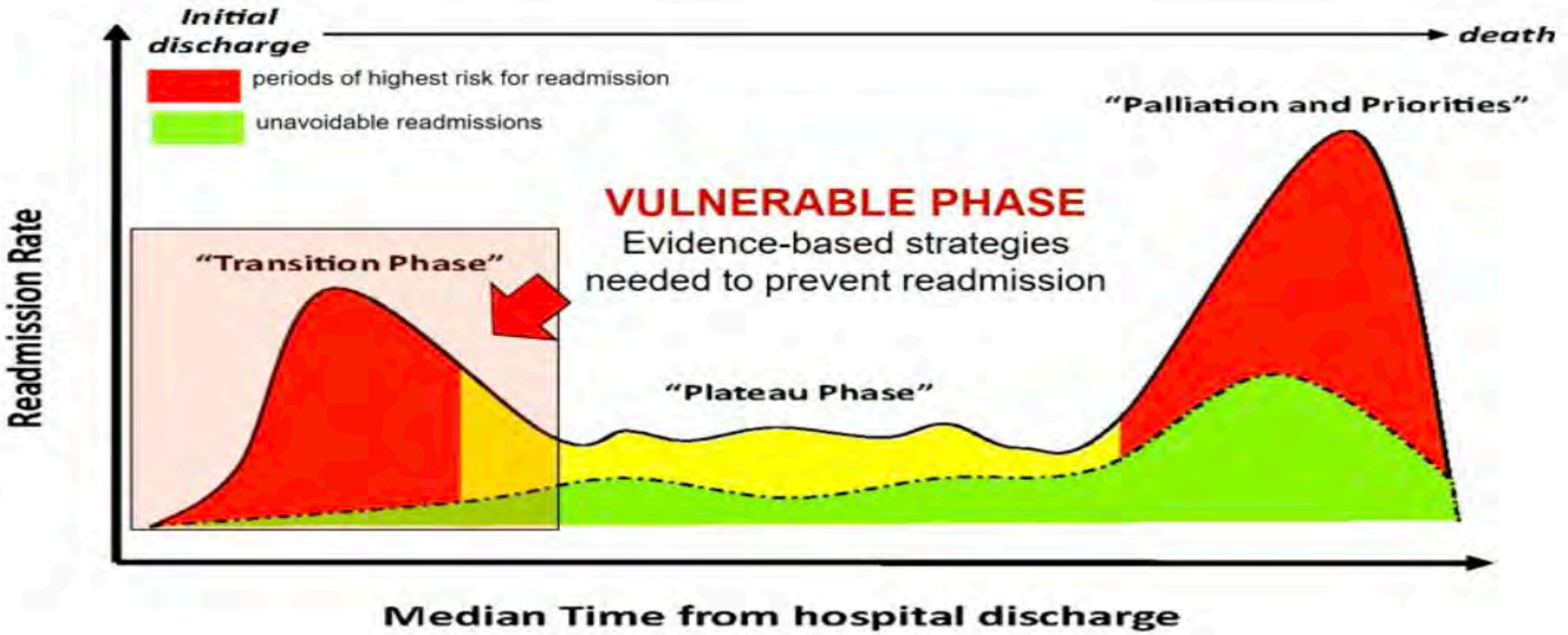
Reavaluar a banda necessitat paracentesi, vasodilatadors, inotrops...albúmina?

Bon fenotipat congestió

European Journal of Heart Failure (2023) doi:10.1002/ejhf.3030

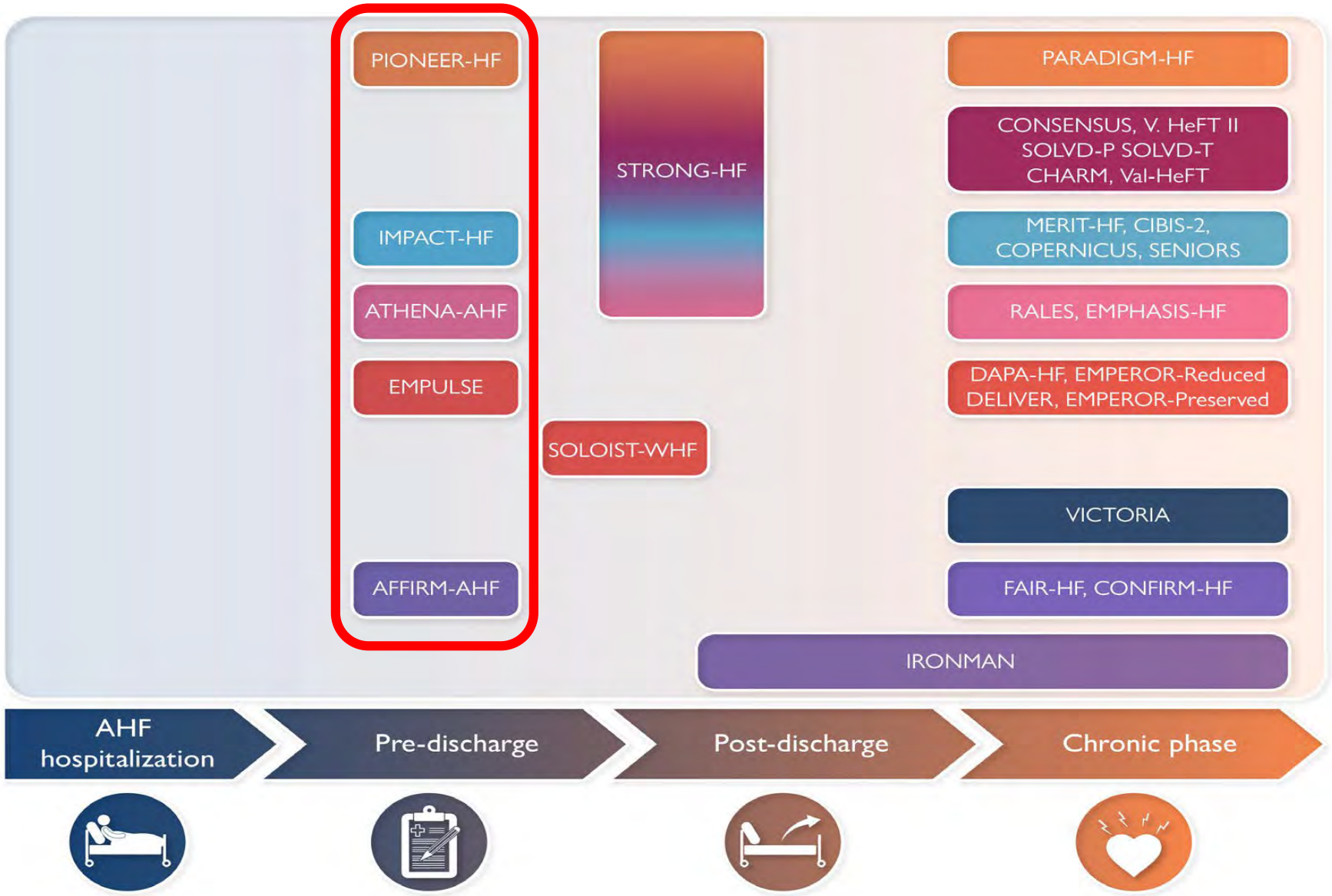
Com organitzo la transició a l'alta?

La fase vulnerable post-ICA



Desai Circulation 2012

Intervencions pre- i post-alta ICA

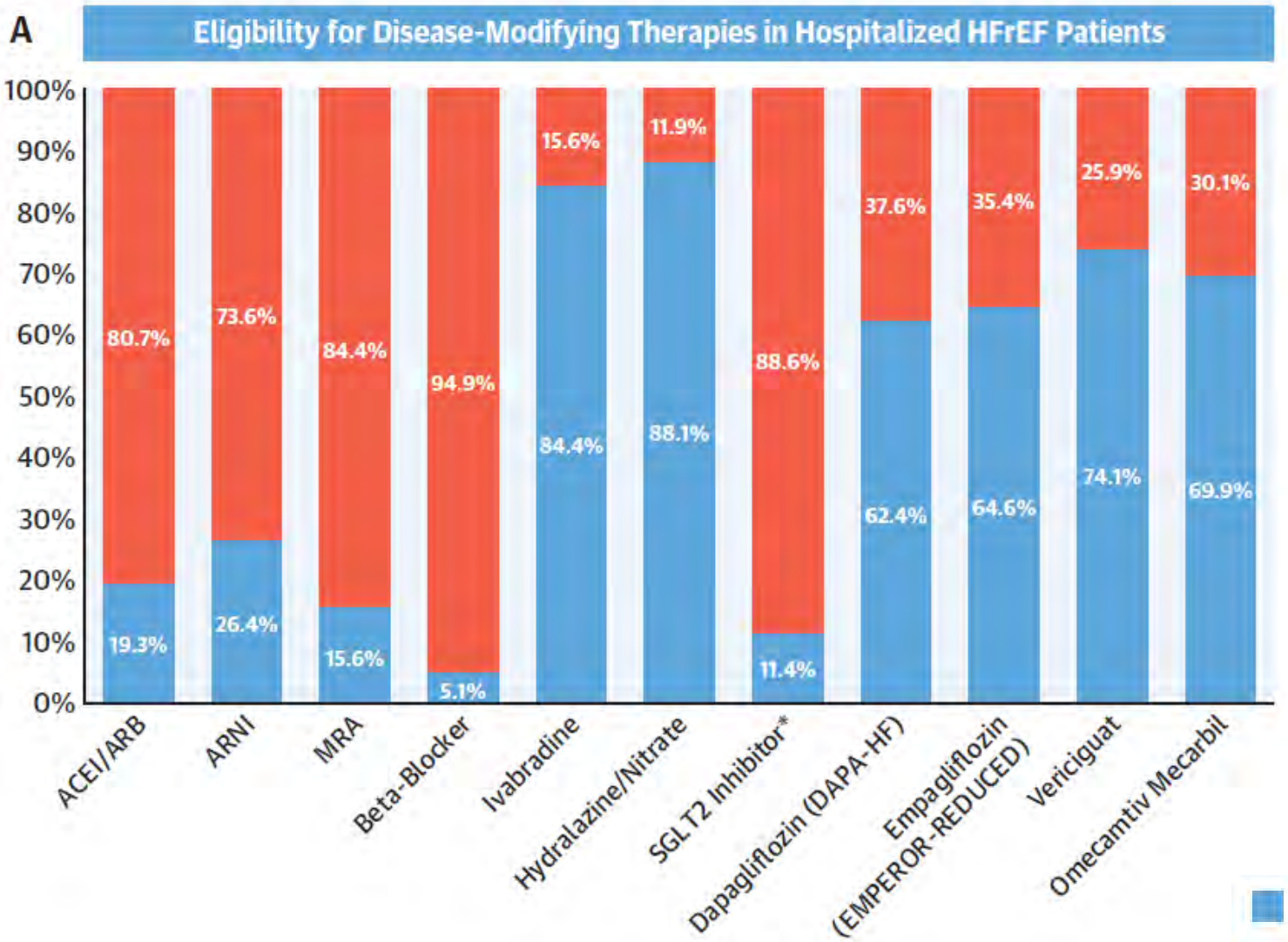


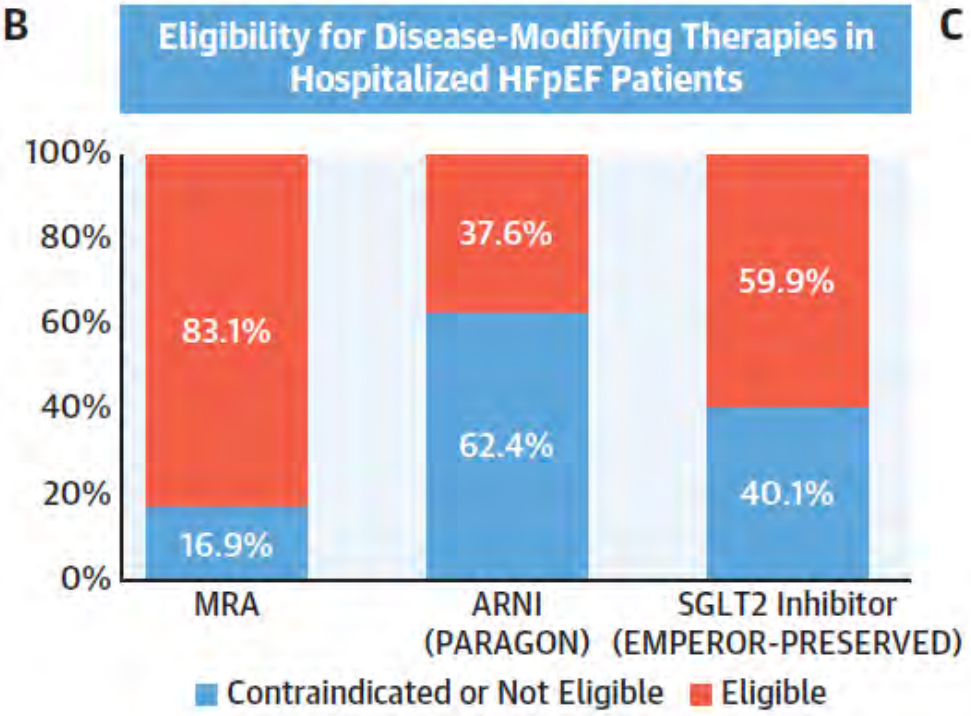
Cap assaig clínic en fase **aguda** ha ofert beneficis en morbimortalitat

Però sí en fase **post-aguda** amb **iSGLT2, ARNI i ARM** (espironolactona)

Metra M. European Journal of Heart Failure (2023) 25, 1115–1131

Quants pacients són bons candidats?





Contraindicated or Not Eligible Eligible

Moghaddam N, et al. J Am Coll Cardiol HF. 2023;11(5):596–606

Estudi STRONG-HF

Recommendation Table 3 — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

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50 anys

Study design

Hospital discharge

Week 1 Safety

Week 2 Safety

Week 3 Safety

Week 6 Safety

Primary endpoint

Main inclusion criteria
- AHF pt ready to be discharged
- No or sub-optimal dose of HF therapies
- Pre-discharge NT-proBNP >1500 pg/ml

Randomise 1:1; n = 1800

High intensity care

Introduction of Half optimal doses of HF therapy

Half optimal doses of HF therapy

Up-titration to Full optimal doses of HF therapy

Full optimal doses of HF therapy

Full optimal doses of HF therapy

90-day follow-up

180-day HF readmission or all-cause mortality

Usual care

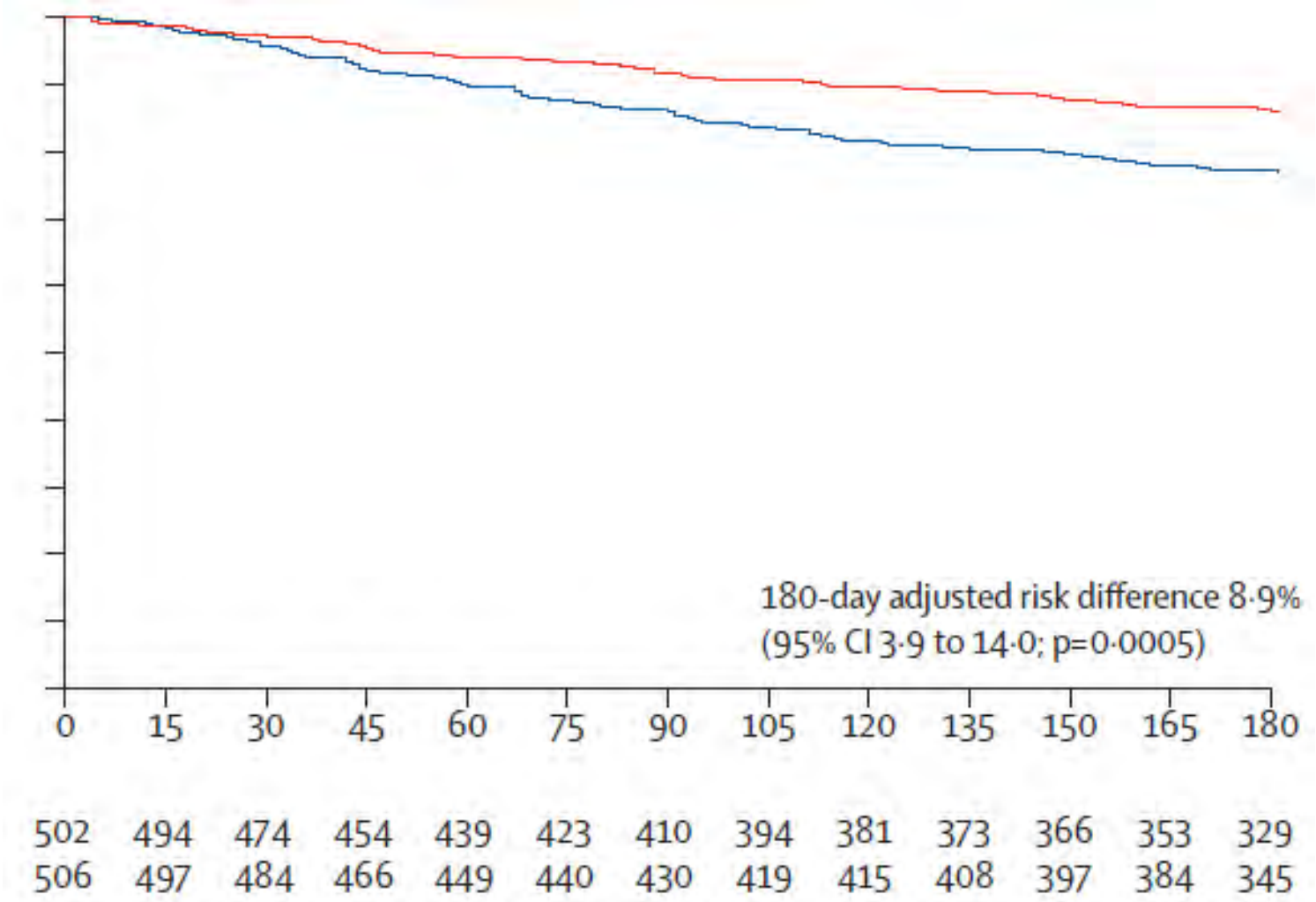
Follow-up and therapy adjustments per physicians usual practice

HF therapy: combining ACEi/ARB/ARNi & BB & MRA
Safety = clinical exam & biology (NT-proBNP, K, Creat, hemoglobin)

Study terminated 23d Sept 2022 by DSMB (n=1069 pt)
- larger than expected difference in primary endpoint
- unethical to keep patients in usual care

Mebazaa Lancet. 2022 Dec 3;400(10367)

Resultats globals



Finalització **precoç** per assoliment de l'objectiu primari: **reingrés per IC + mortalitat x qualsevol causa** a **6** mesos

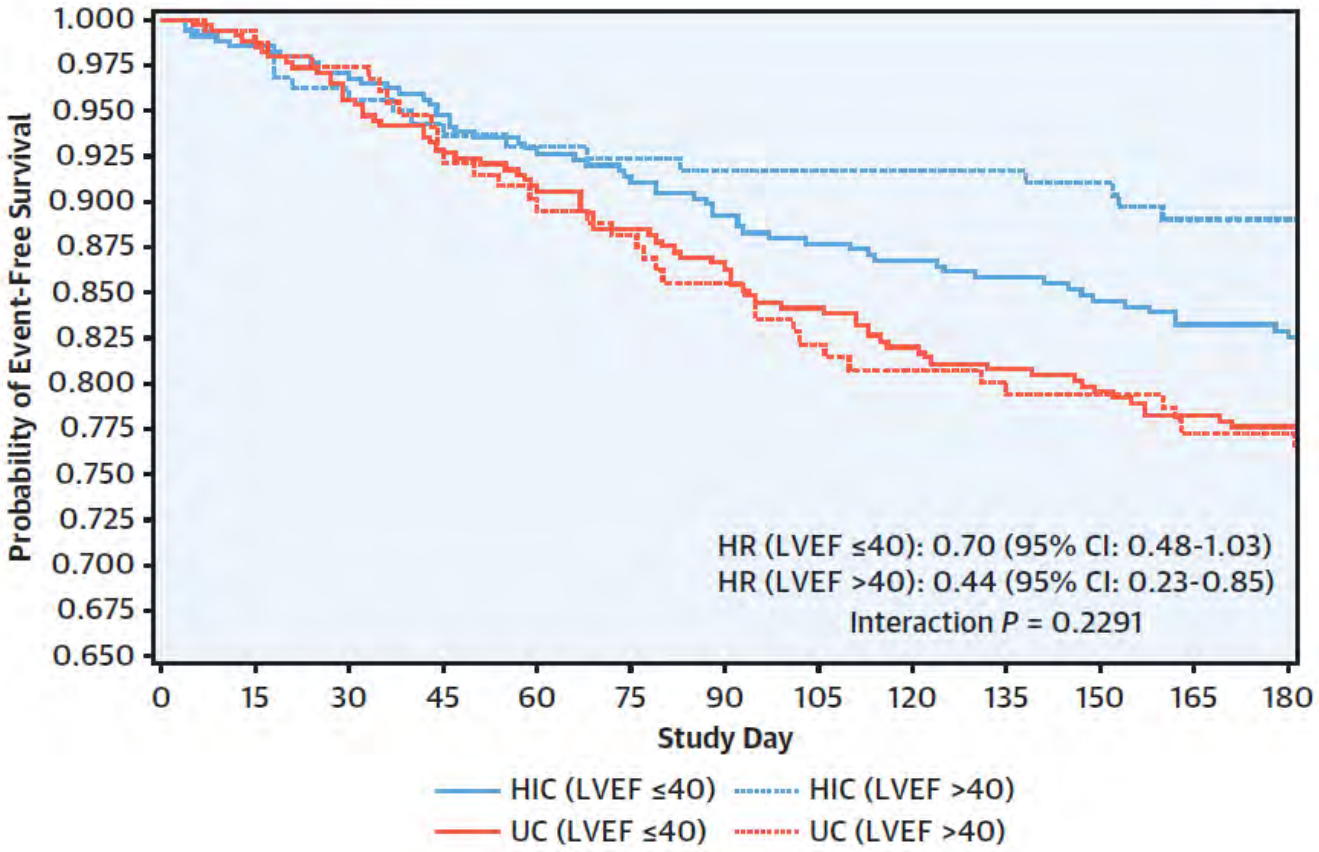
Objectiu principal: **diferència en RR ajustat 8,9%** (15,2 vs 23,3% = reducció 33% del risc relatiu)

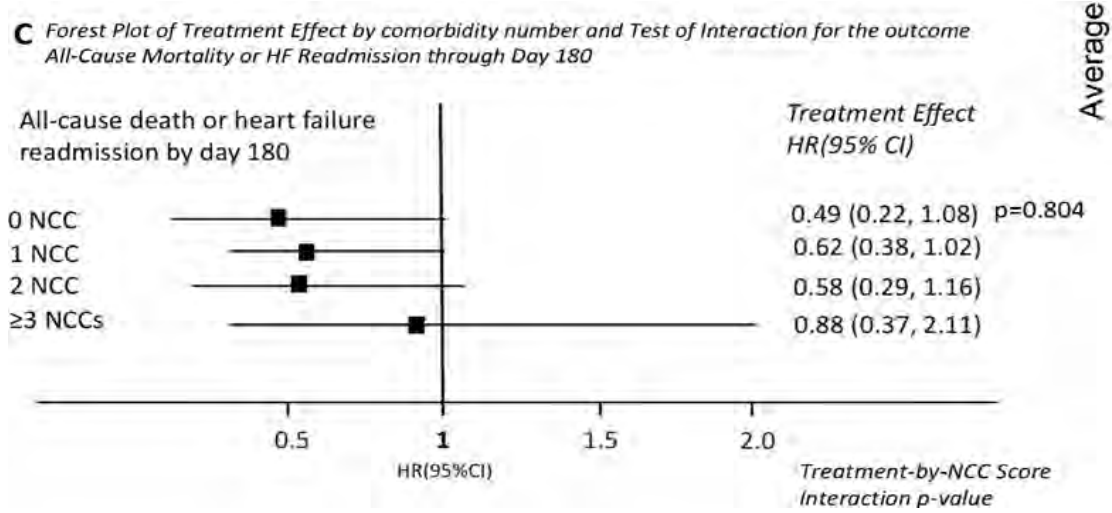
Objectius secundaris: **millora QV i reingrés IC 180d** també assolits

Mebazaa Lancet. 2022 Dec 3;400(10367)

En funció de FEVI i comorbiditat

Tot i que de manera més atenuada, el protocol STRONG-HF **redueix significativament també** el risc de mort + reingrés en pacients amb **FEVE > 40%**

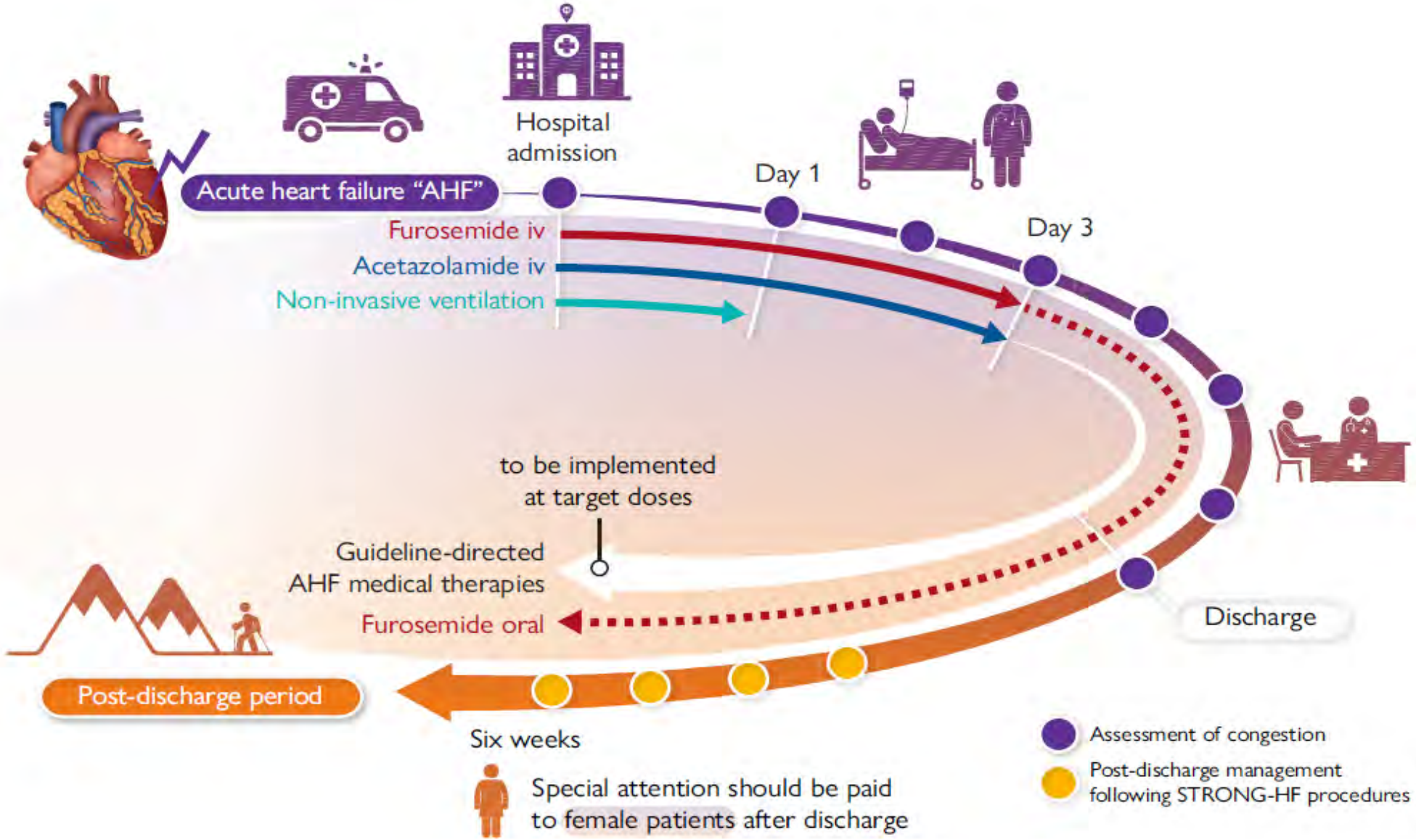




En pacients amb 1 o 2 comorbiditats no "cardíaques" també es manté l'efecte protector

J Am Coll Cardiol 2023;81:2131–2144
European Journal of Heart Failure (2023) doi:10.1002/ejhf.3039

Resum fase aguda i postaguda

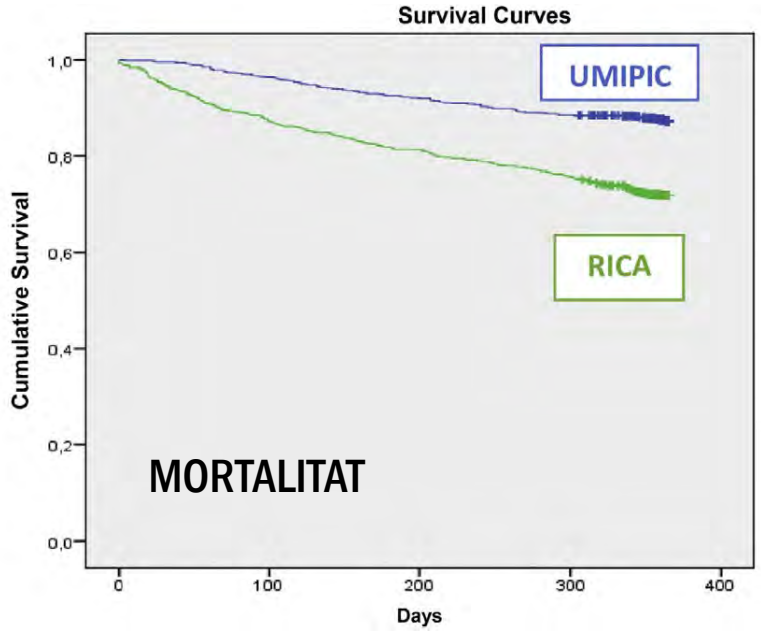


Deniau B. European Heart Journal (2023) 44, 4634–4649

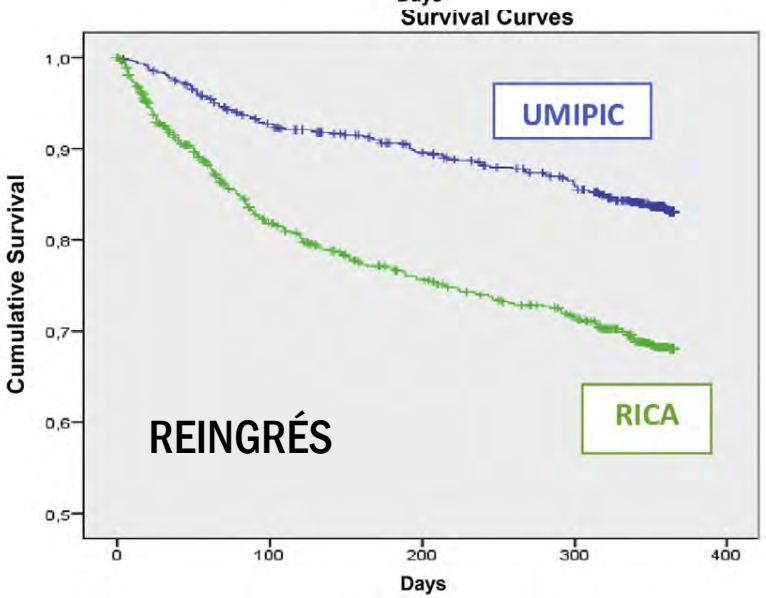
Transició a l'alta

Anguita M, et al. Rev Esp Cardiol Supl. 2020;20(B):1-46

Seguiment estructurat: exemples

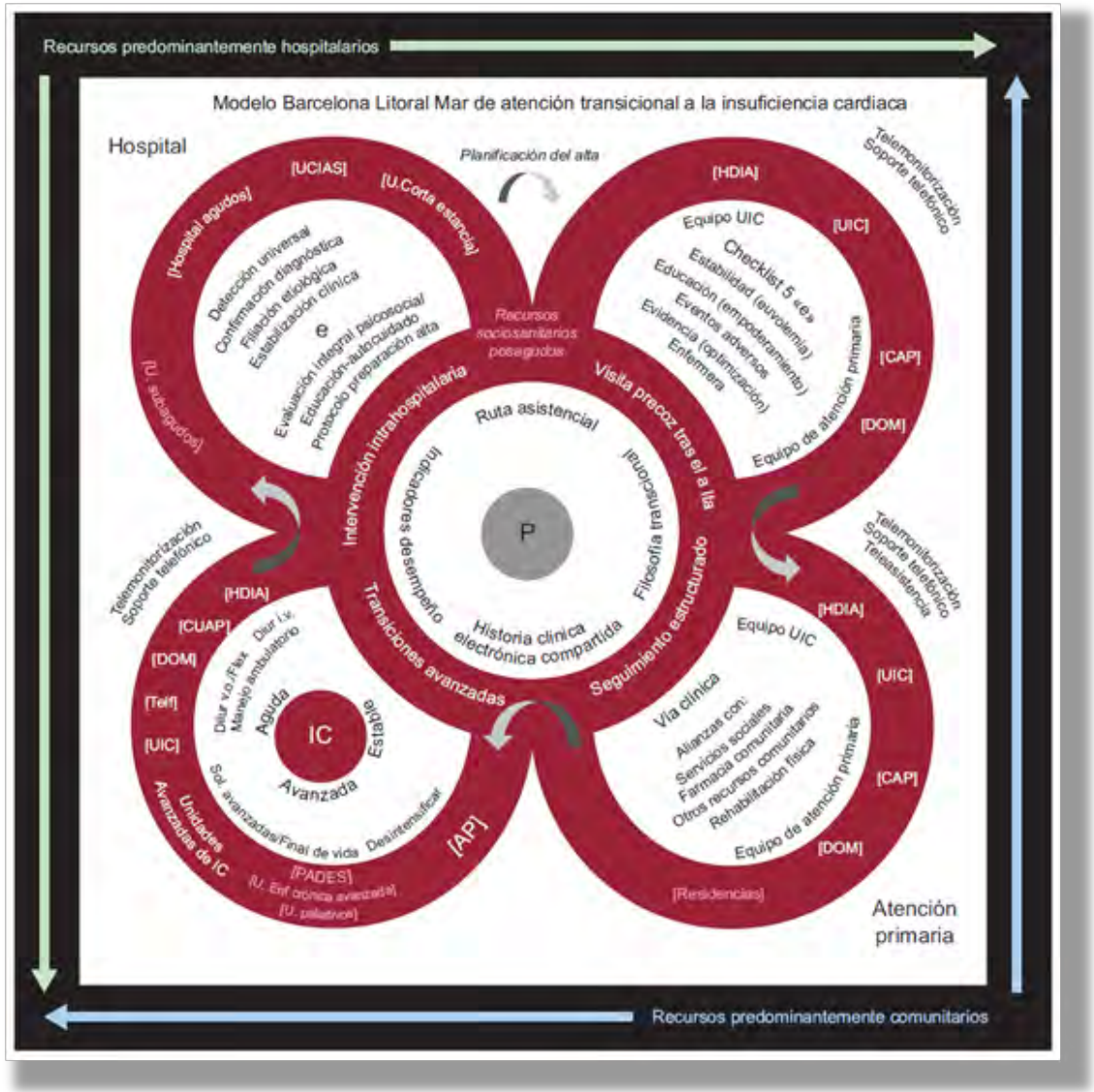


UMIPIC
Unidades de Manejo Integral de Pacientes con Insuficiencia Cardiaca



HOSPITAL UNIVERSITARI DE BELLVITGE
SERVEI DE CARDIOLOGIA

PROJECTE DE GESTIÓ DE LA SECCIÓ D' INSUFICIÈNCIA CARDIACA CRÒNICA



Comin-Colet Rev Esp Cardiol 2016
González-Franco Rev Clin Esp 2022;222:339-47

Alguna pregunta més?