



Actualització en patologies mèdiques prevalents

Insuficiència cardíaca

Insuficiència cardíaca amb Fracció d'ejecció del ventricle esquerre preservada: aspectes diagnòstics i tractament específic.



Hospital Universitari
Mútua Terrassa

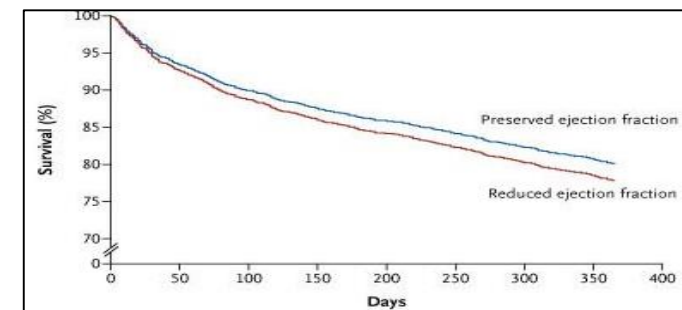
Epidemiologia de la insuficiència cardíaca amb FEVIp



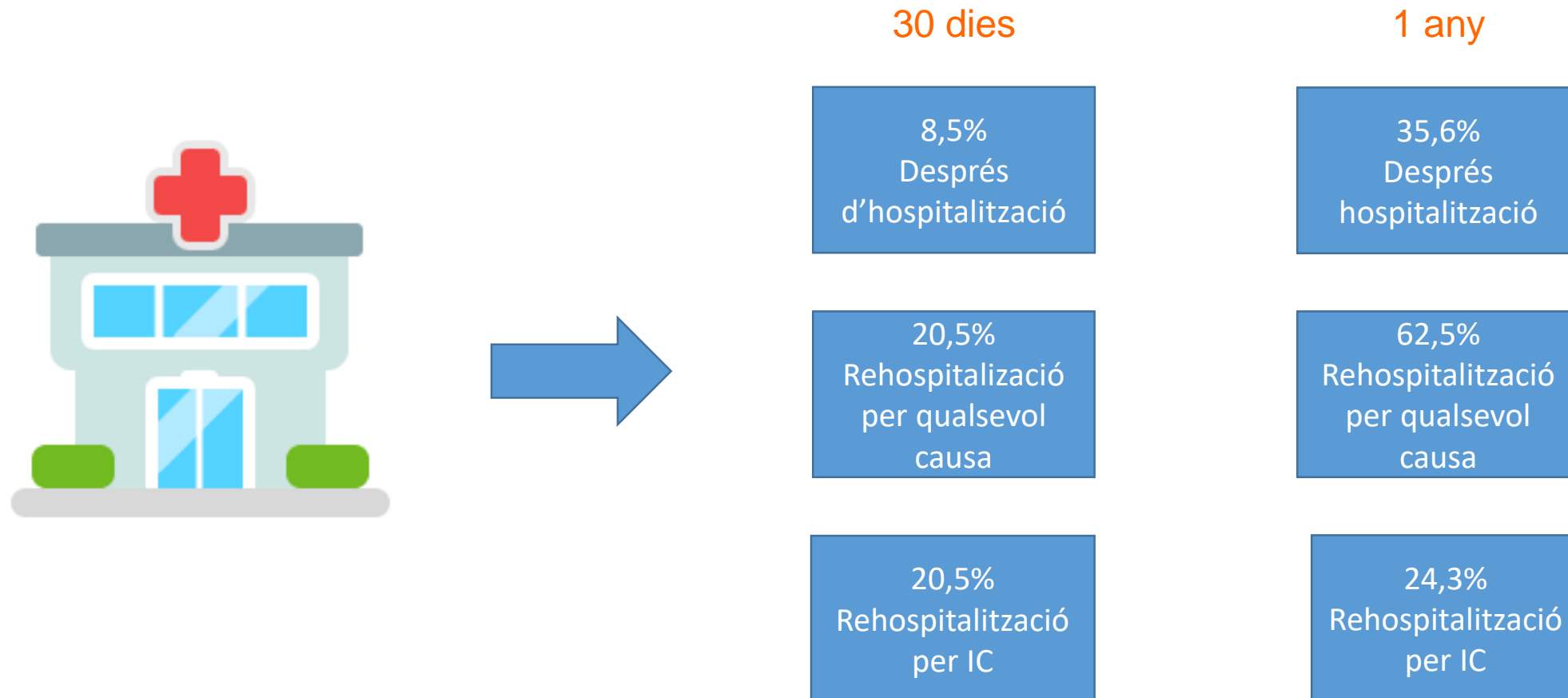
- La **prevalença** és **1,1-5,5%** en població general.
- És més freqüent en **dones**, i s'associa a **obesitat, hipertensió arterial** i genera major dependència funcional.
- Registres de USA/UE/Àsia demostren que **35-50% dels pacient amb ICA** hospitalitzats presenten IC FEVIp



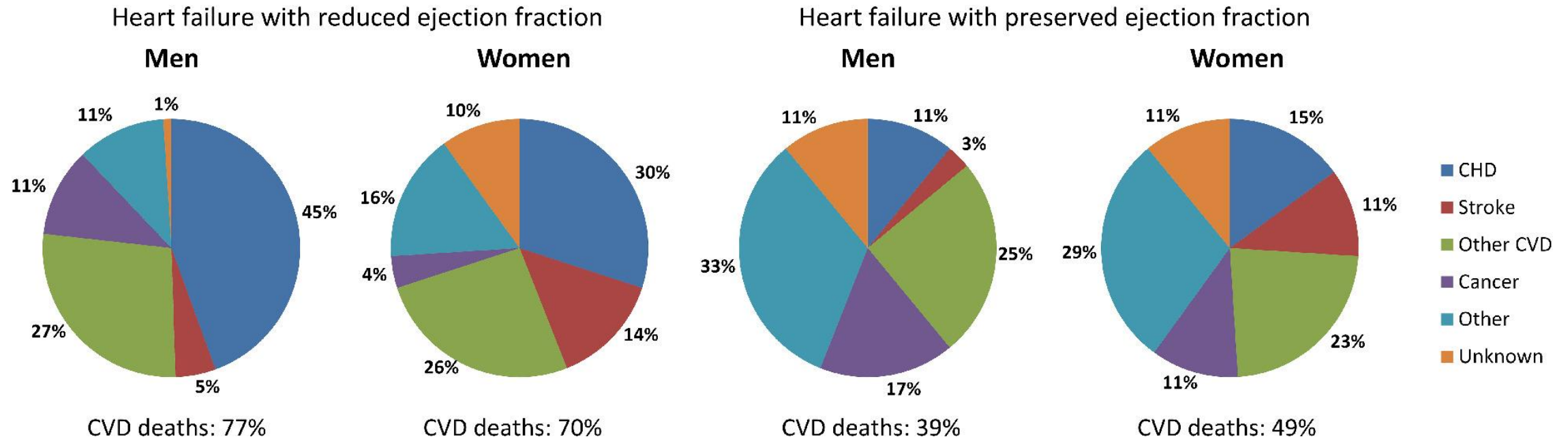
- La mortalitat és similar a la reduïda
- Aproximadament el 30% dels pacients amb IC i FEVI preservada moren durant el primer any de diagnòstic



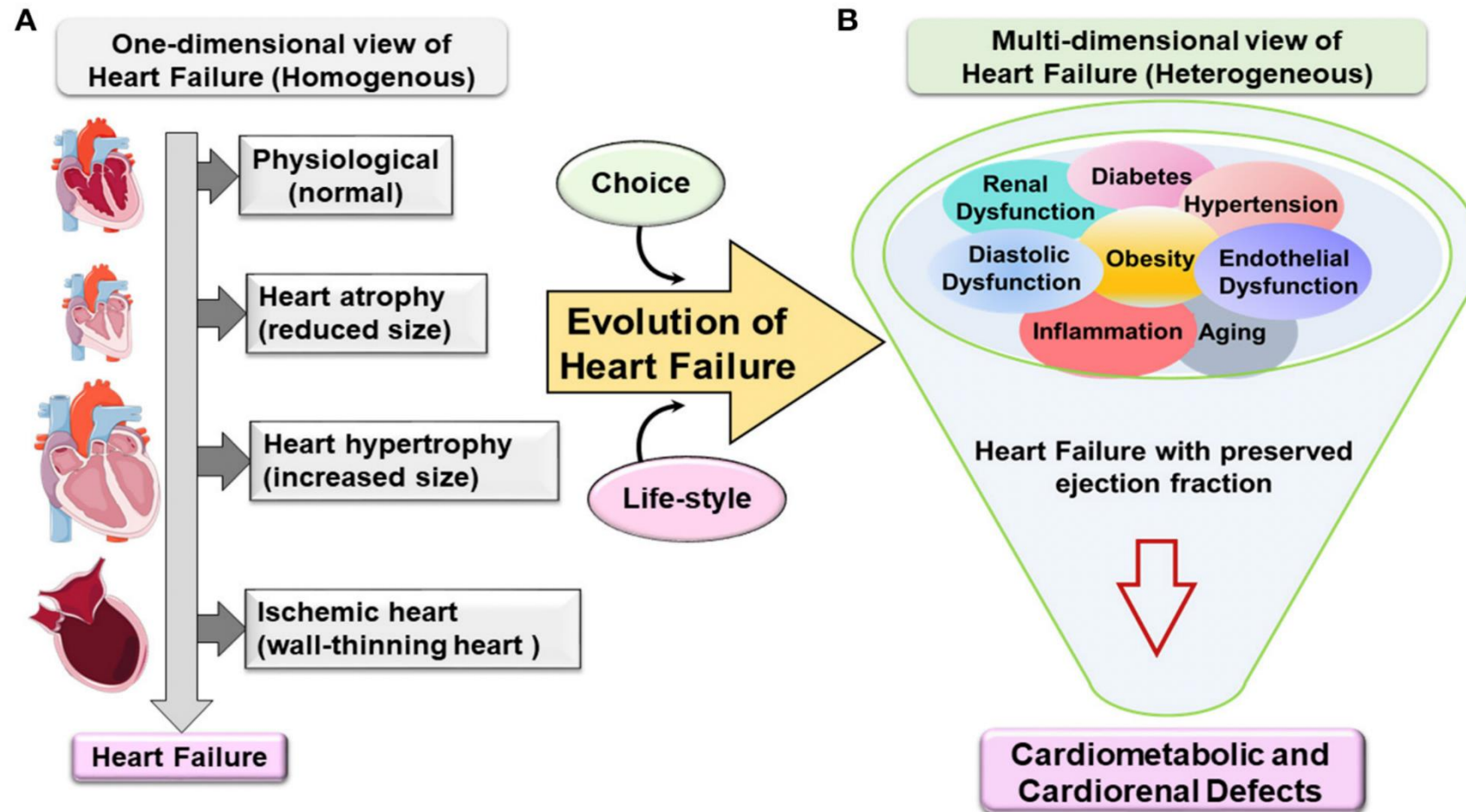
Epidemiologia: Impacte dels reingressos en IC amb FEVIp



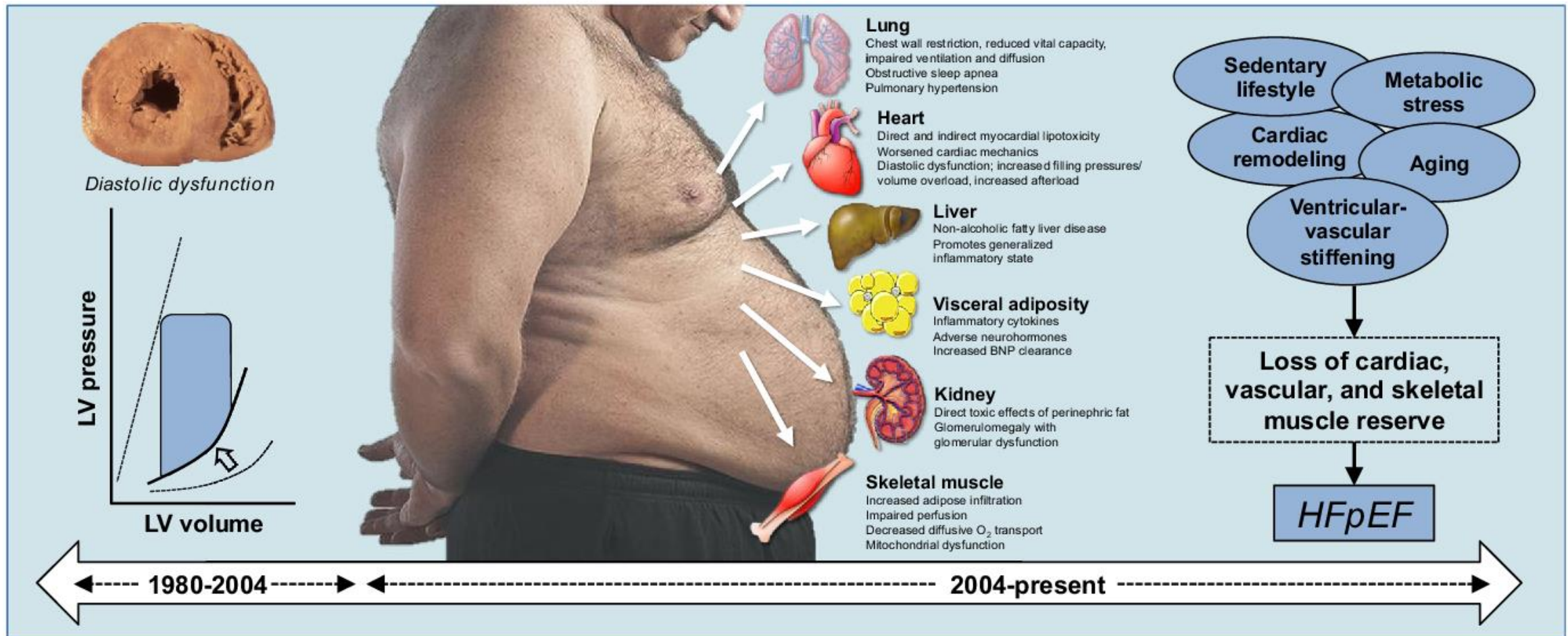
Causes de mort en IC FEVIp



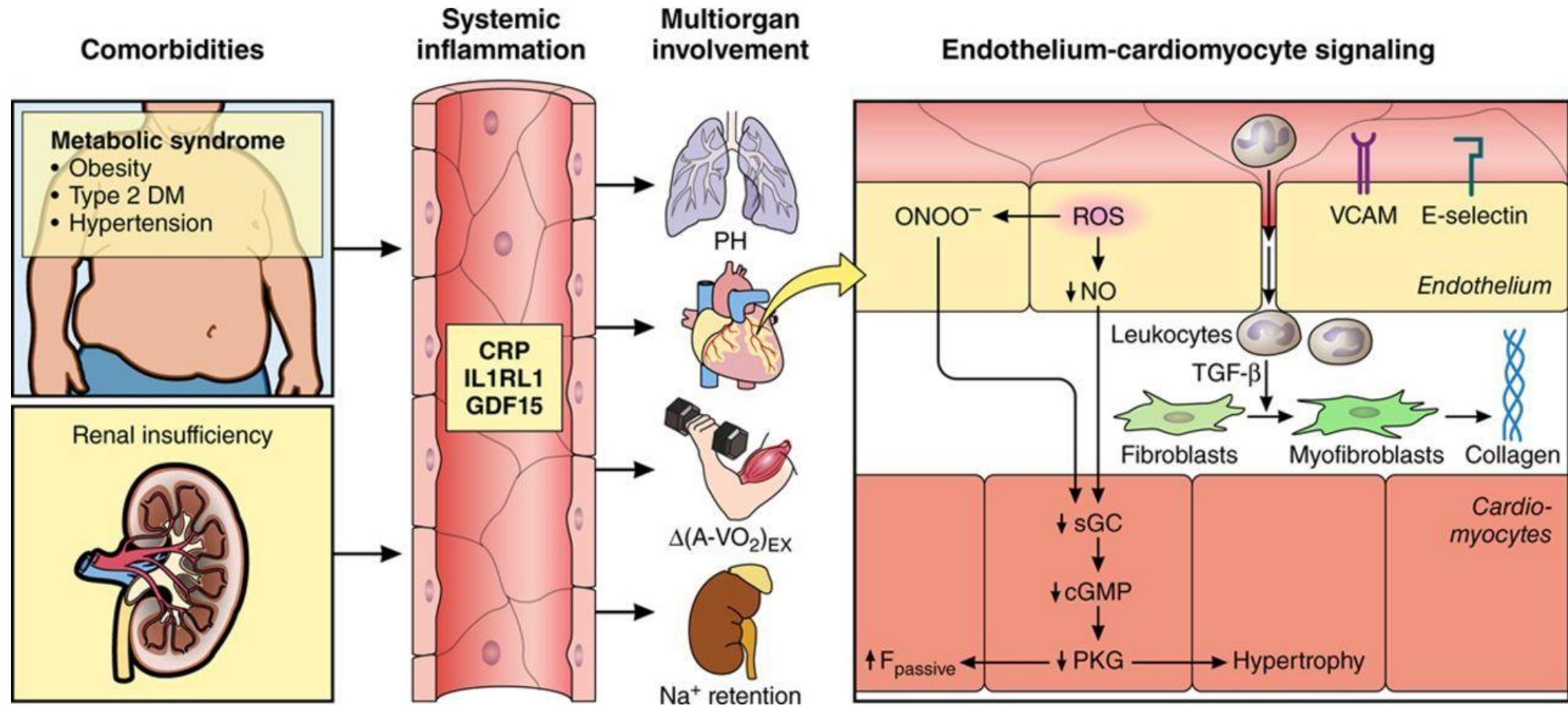
Visió multidimensional de la IC amb FEVIp



IC preservada com a malaltia sistèmica



Fisiopatologia: inflamació sistèmica



Definició de IC

Table 1. HF Definitions in Contemporary Clinical Practice Guidelines.

ACCF/AHA (2013) ³	HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue.
ESC (2016) ⁴	HF is a clinical syndrome characterized by typical symptoms (eg, breathlessness, ankle swelling and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.
JCS/JHFS (2017) ⁵	HF is a clinical syndrome consisting of dyspnea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart.

Falta d'homogeneïtat entre les diferents guies de pràctica clínica
Diferents criteris d'inclusió als assajos clínics.



Definició de IC

Consensus Statement

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association

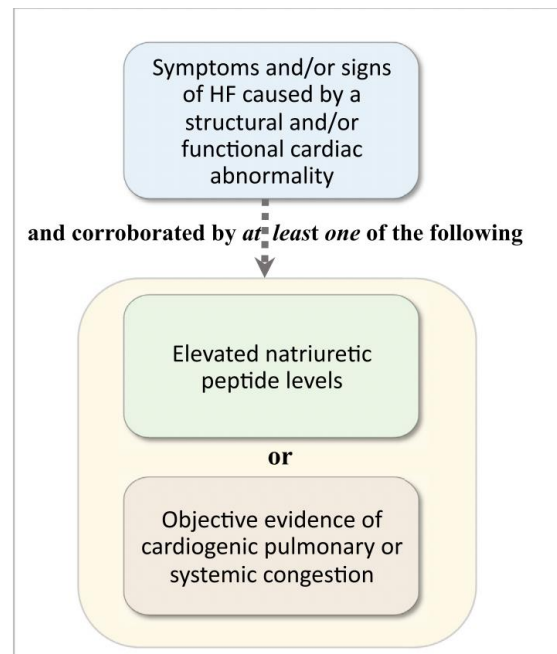


Figure 1. Universal definition of HF.

Table 6. Symptoms and Signs of HF

Symptoms of HF

- Typical
- Breathlessness
 - Orthopnea*
 - Paroxysmal nocturnal dyspnea*
 - Reduced exercise tolerance*
 - Fatigue, tiredness[†]
 - Ankle swelling*
 - Inability to exercise*
 - Swelling of parts of the body other than ankles
 - Bendopnea
- Less typical
- Nocturnal cough
 - Wheezing
 - Bloated feeling[‡]
 - Postprandial satiety[‡]
 - Loss of appetite
 - Decline in cognitive function, confusion (especially in the elderly)[†]
 - Depression
 - Dizziness, syncope[†]

Signs of HF

- More specific
- Elevated jugular venous pressure*
 - Third heart sound*
 - Summation gallop with third and fourth heart sounds
 - Cardiomegaly, laterally displaced apical impulse
 - Hepatojugular reflux
 - Cheyne Stokes respiration in advanced HF[†]
- Less specific
- Peripheral edema (ankle, sacral, scrotal)
 - Pulmonary rales*
 - Unintentional weight gain (>2 kg/week)
 - Weight loss (in advanced HF) with muscle wasting and cachexia
 - Cardiac murmur
 - Reduced air entry and dullness to percussion at lung bases suggestive of pleural effusion
 - Tachycardia, irregular pulse
 - Tachypnea
 - Hepatomegaly/ascites
 - Cold extremities[†]
 - Oliguria
 - Narrow pulse pressure

*Commonly used in clinical trials, registries, risk scoring, and have been tested for sensitivity and specificity.

[†]Common in low perfusion, low cardiac output states.

[‡]Can be typical in the setting of right HF or biventricular failure.



Definició IC FEVIp

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤40%	LVEF 41 – 49% ^b	LVEF ≥50%
	3	—	—	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c

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HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

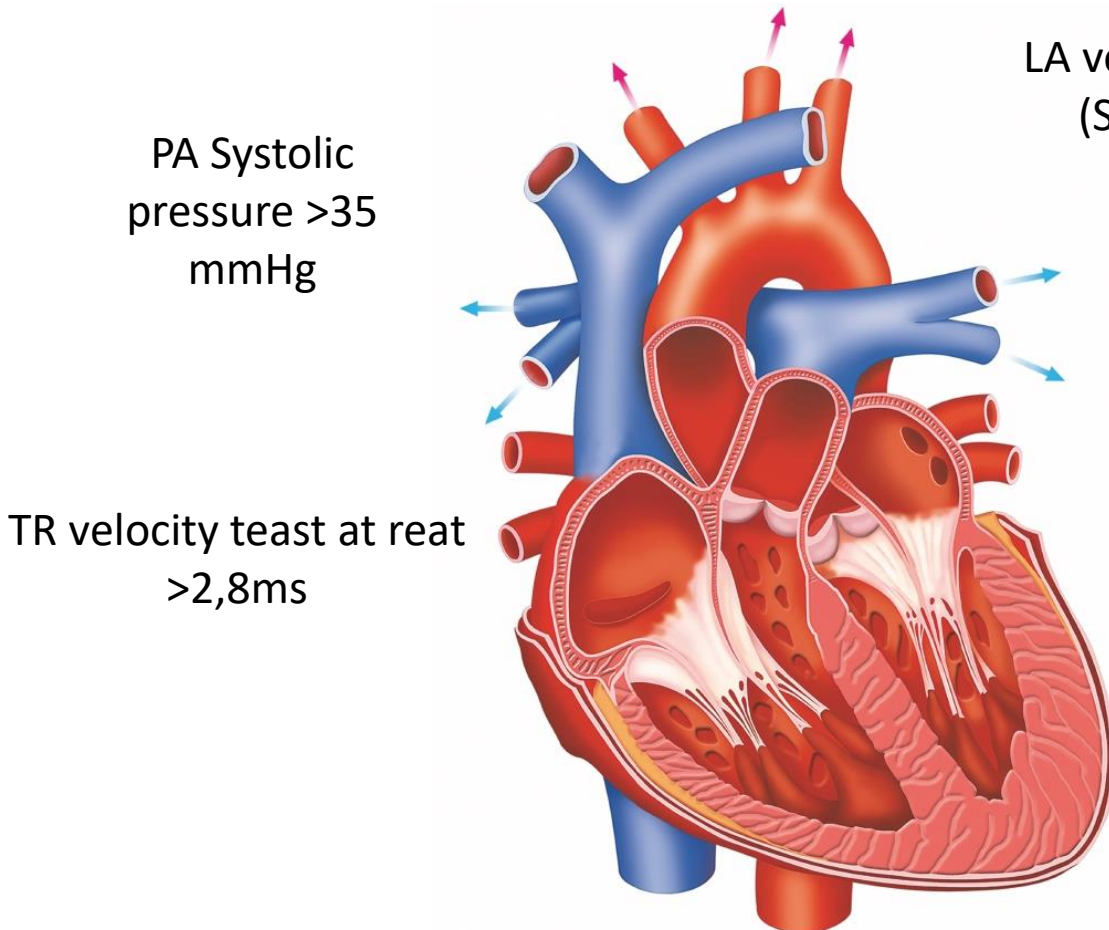
^aSigns may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

^bFor the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

^cFor the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.



Definició IC FEVIp



PA Systolic
pressure >35
mmHg

TR velocity teast at reat
>2,8ms

LA volumen index >34mL/m²
(SR) or >40 mL/m² (AF)

E/e' ratio at rest >9

Relative Wall thickness >0,42

LV mass index >95 pg/m² (female) or >115 pg/m²

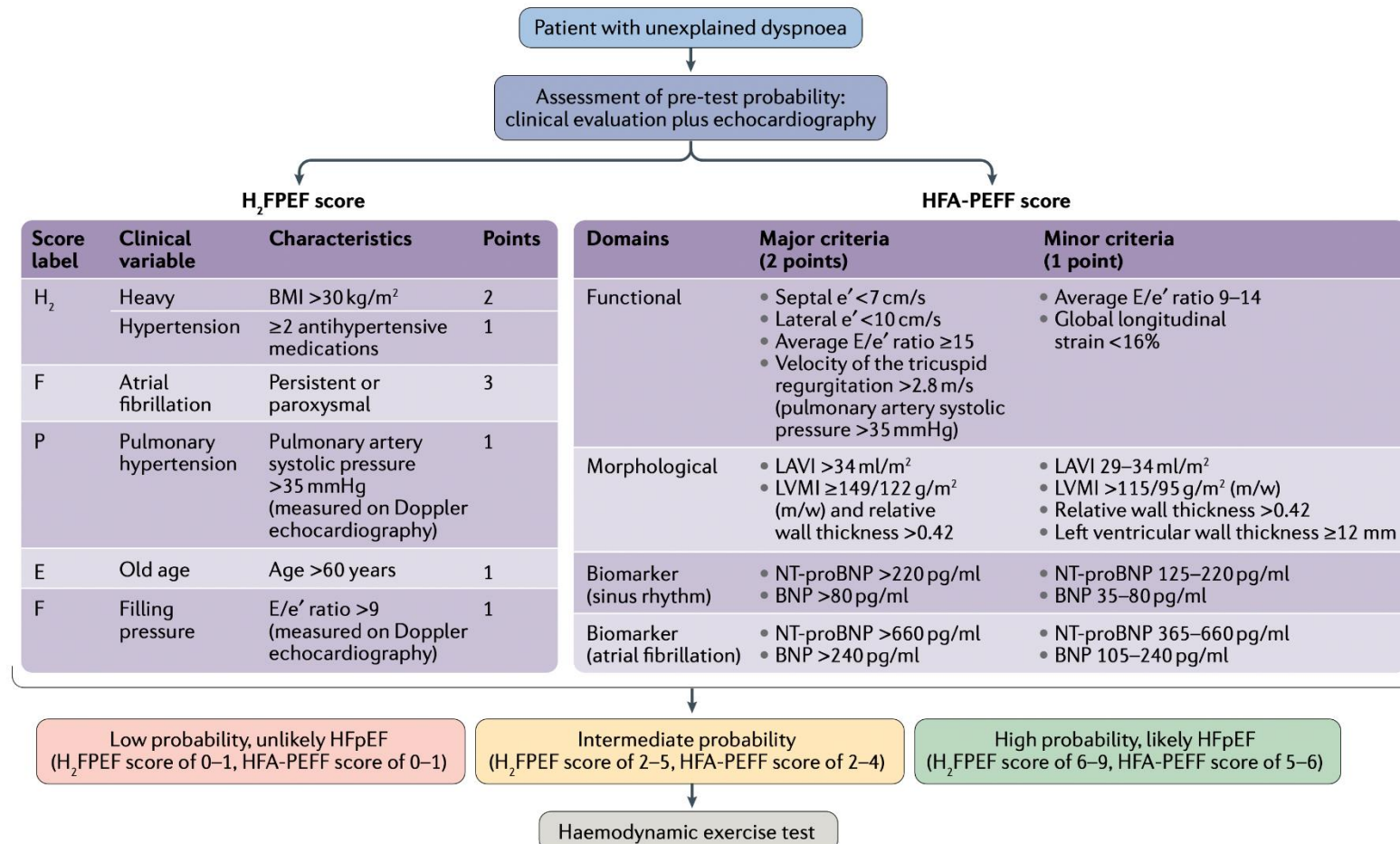


NT-proBNP
<125 pg/ml (SR) or >365pg/ml (AF)
BNP
>35pg/ml (SR) or 105 pg/ml (AF)



Diagnòstic de FEVIp: SCORES

Clinical Variable	
H₂	Heavy
	Hypertensive
F	Atrial Fibrillation
P	Pulmonary Hypertension
E	Elder
F	Filling Pressure
H₂FF	
Total Points	0 1
Probability of HFpEF	0.2 0.



Biomarker (AF)	
NT-proBNP > 660 pg/ml or BNP > 240 pg/ml	
NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml	
Haemodynamic Measurements	



Tractament no específic de la IC amb FEVIp

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

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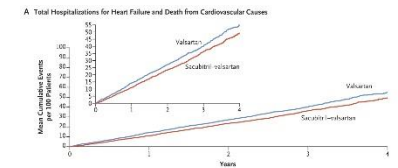
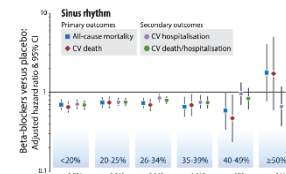
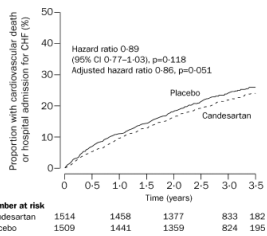
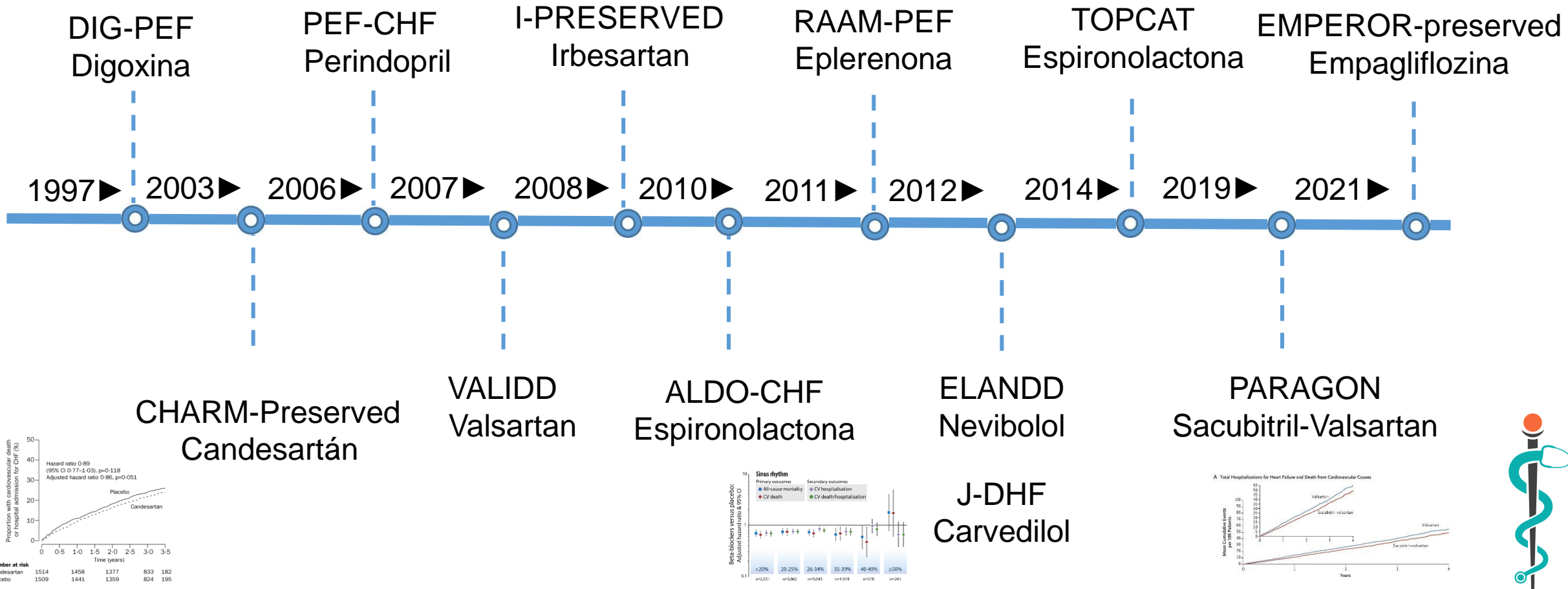
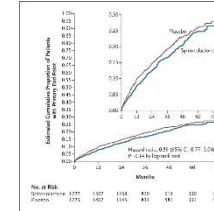
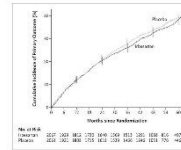
Tractament de la comorbiditat

Associations Between Preserved Ejection Fraction (HFpEF) and Reduced Ejection Fraction (HFrEF), With Comorbidities

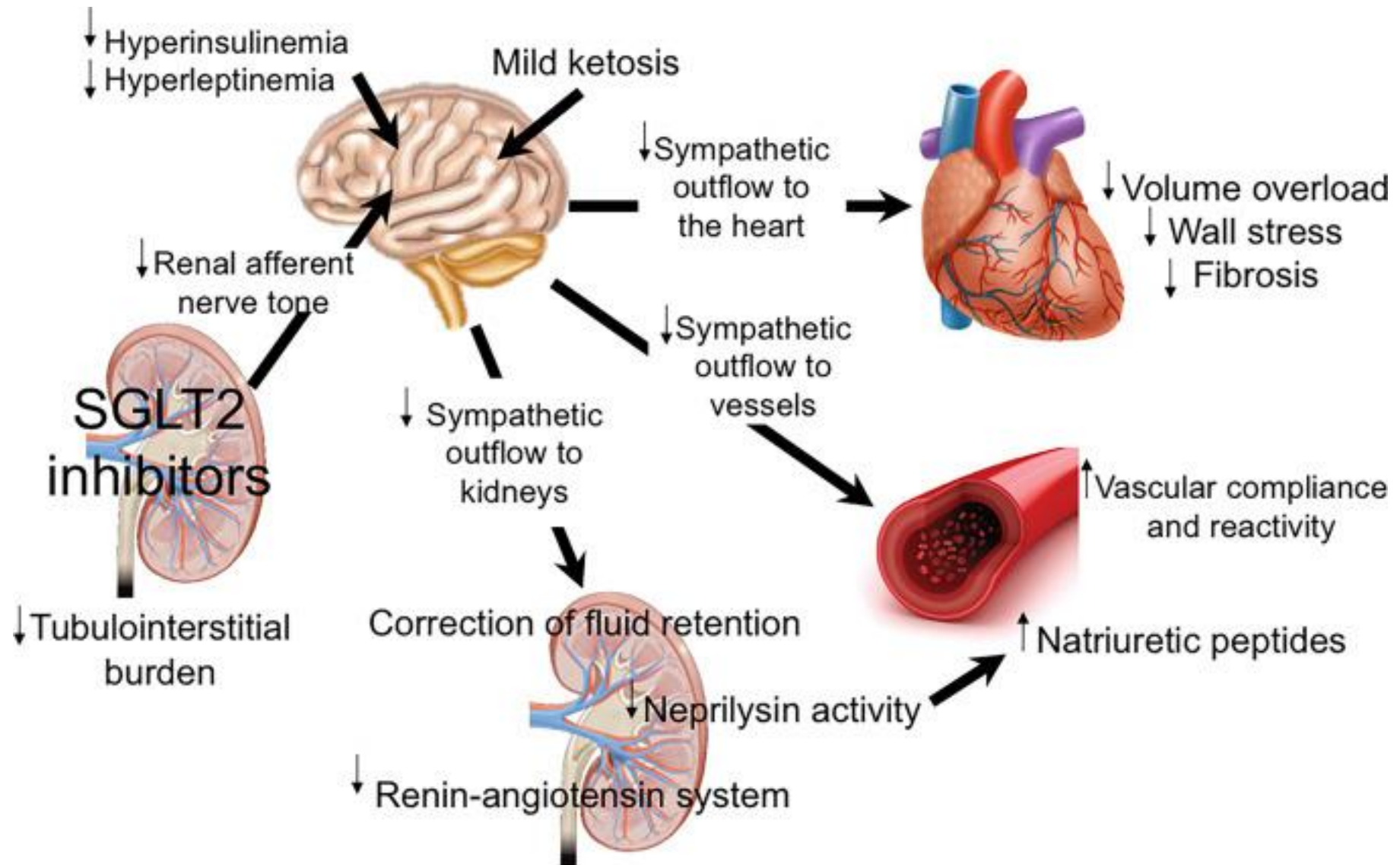
<p>Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects</p> <p>Elevated LV end diastolic pressure and beta-blocker use may compromise lung function</p>	<p>More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF)</p> <p>Higher mortality risk in HFpEF</p>
<p>Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines</p> <p>Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate</p>	<p>More prevalent in HFpEF</p> <p>Similar increased risk for mortality in both groups</p>
<p>Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease</p> <p>Incident and worsening diabetes mellitus via sympathetic and RAAS activation</p>	<p>More prevalent in HFpEF</p> <p>Similar increased risk for mortality in both groups</p>
<p>Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation</p> <p>Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure</p>	<p>Similar prevalence in both groups</p> <p>Similar increased risk for mortality in both groups</p>
<p>Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion</p> <p>Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system</p>	<p>Similar prevalence in both groups</p> <p>Unknown mortality differential associated with HFpEF vs. HFrEF</p>
<p>Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus</p> <p>Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies</p>	<p>More prevalent in HFpEF</p> <p>Obesity paradox; potential for a U-shaped association with mortality</p>



Principals assajos clínics en IC FEVI preservada



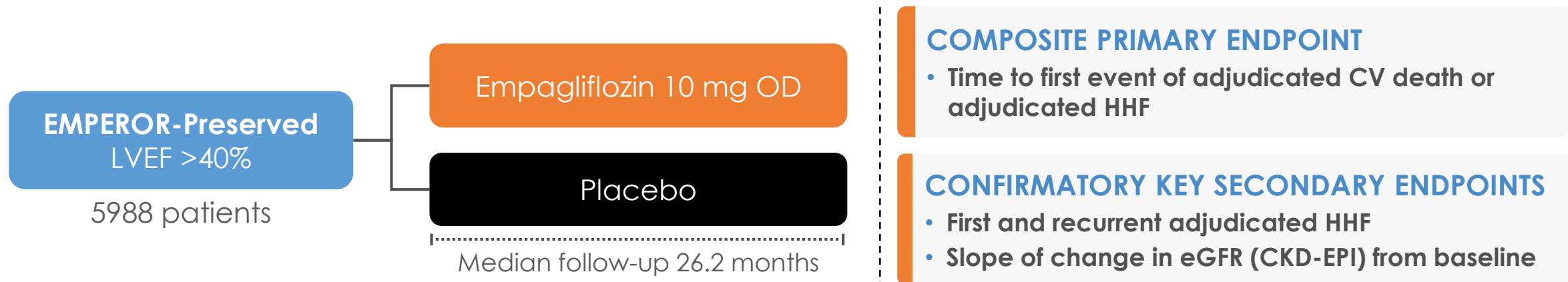
iSGLT2



EMPEROR-preserved: disseny del estudi

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with **preserved ejection fraction**

Population: T2D and non-T2D, aged ≥ 18 years, chronic HF (NYHA class II–IV)

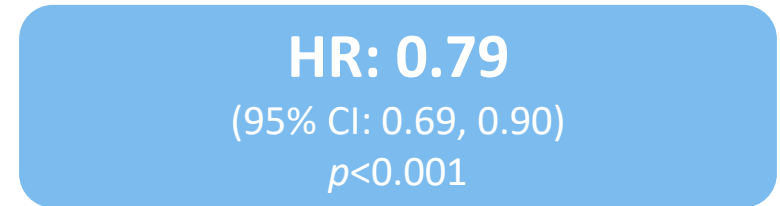
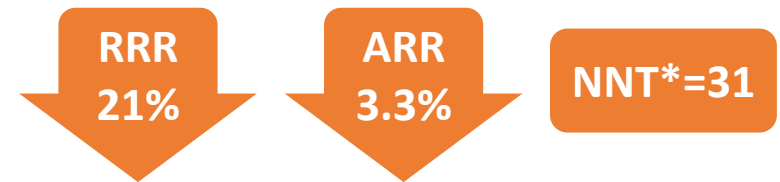
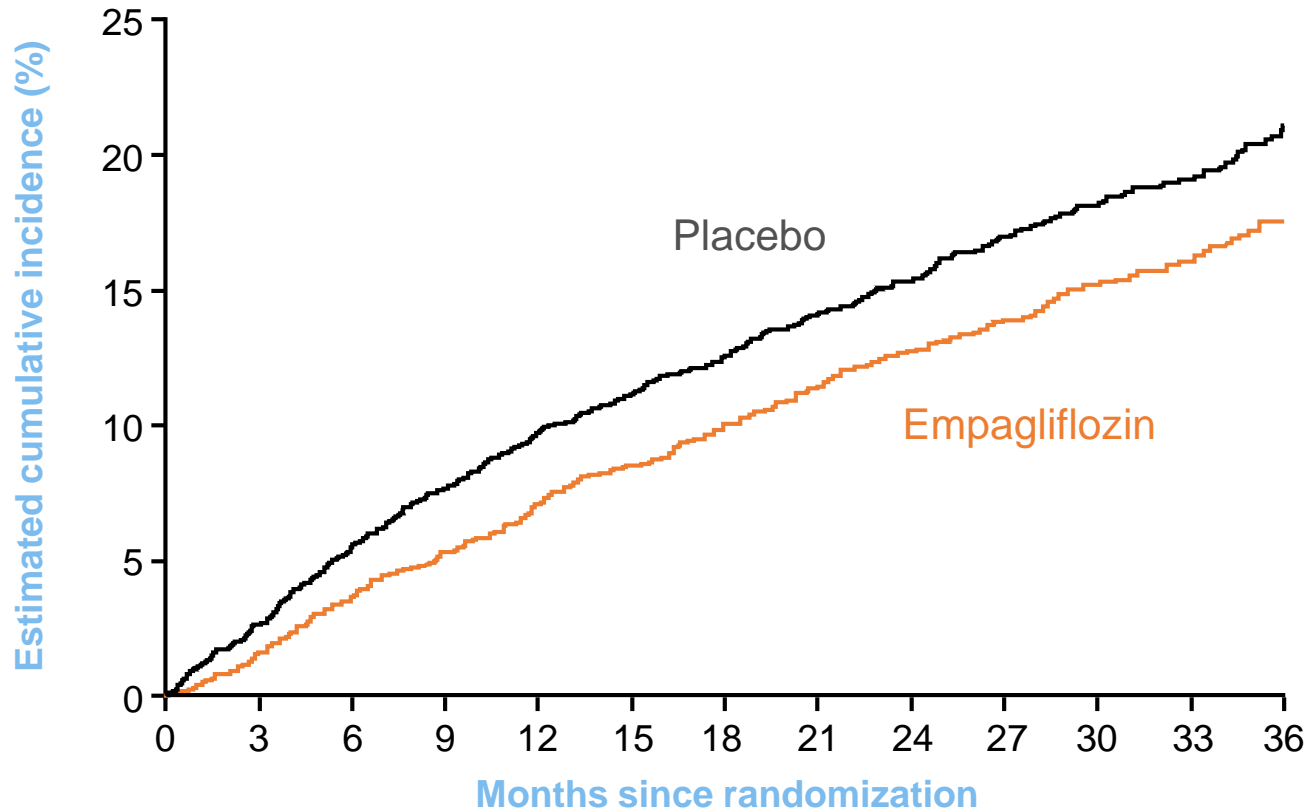


*Randomized, double-blind, placebo-controlled trial.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; OD, once daily.
Anker S et al. *N Engl J Med.* 2021;XX:XXX.



Empaglifozina en IC amb FEVI preservada



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

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; 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: End-points

EMPEROR-Preserved



Primary endpoint:
Adjudicated CV death or
HHF

Confirmatory*

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



Key secondary endpoint:
Adjudicated first and recurrent
HHF

Confirmatory[†]

HR: 0.73
(95% CI: 0.61, 0.88)
 $p < 0.001$



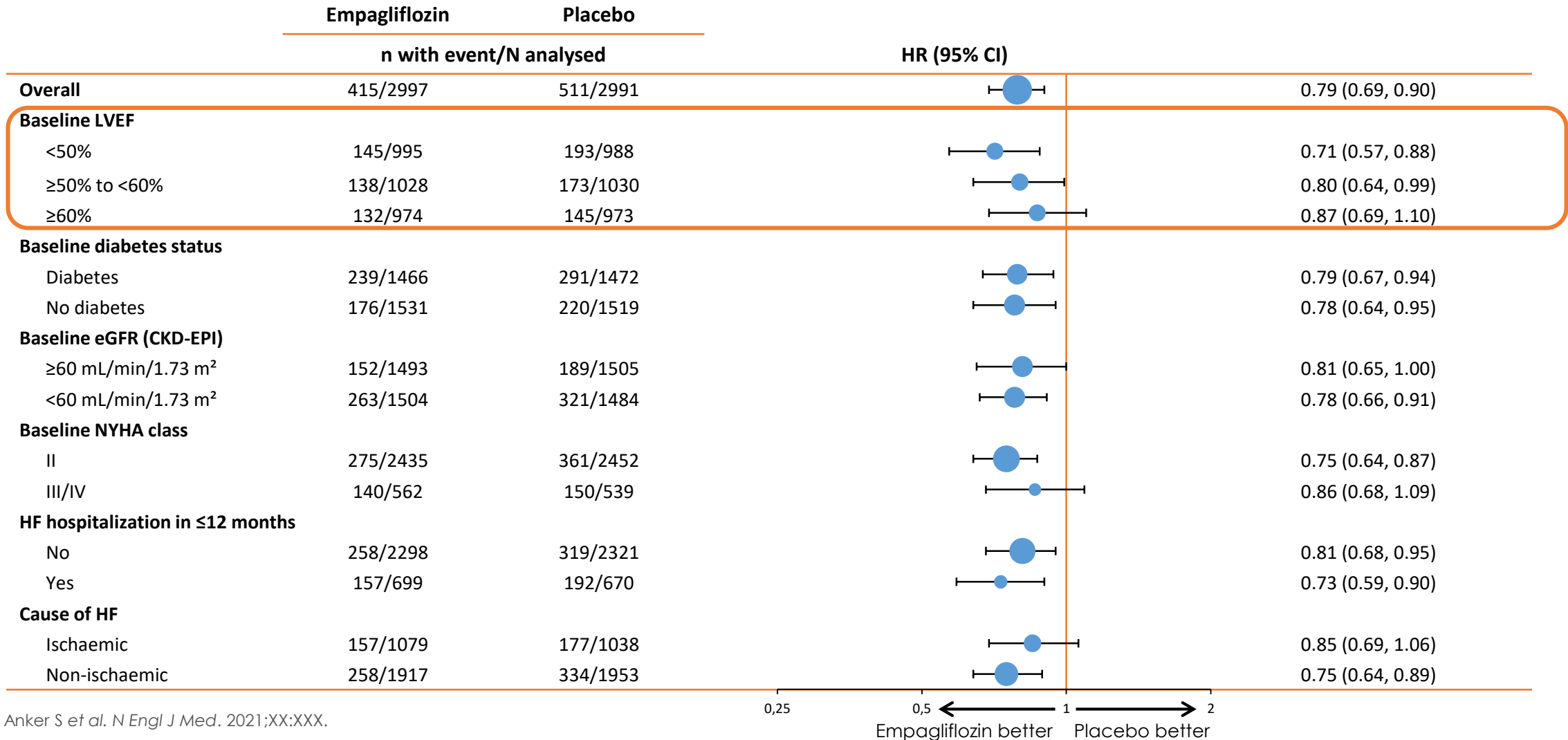
Key secondary endpoint:
eGFR slope

Confirmatory[‡]





+1.36
mL/min/1.73 m² per year
 $p < 0.001$



Empagliflozina en IC amb FEVI preservada

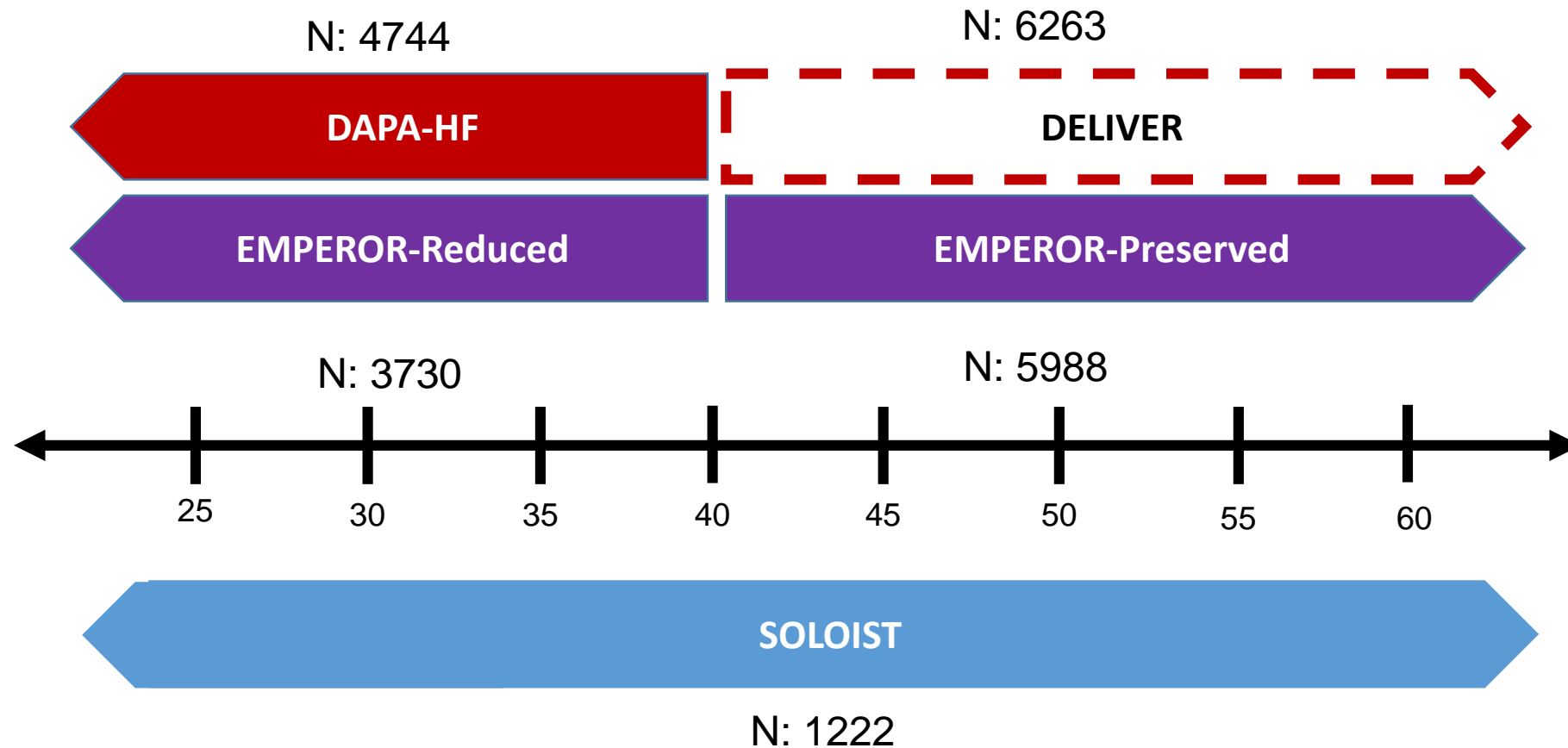


EMPEROR-preserved: End-points en grups estratificats per FEV1p

		FEV1 >50%
	Endpoint primari: Mort CV o ingrés per IC	↓ 17% <i>P 0.024</i>
	Endpoint secundari: Ingrés per IC (primera hospitalització per IC)	↓ 22% <i>P 0.013</i>
	Qualitat de vida KCCQ-CSS	1.46 punts de milloria
	Funció renal: eGFR slope	+1.24mL/min/1.73m ² per year <i>p<0.001</i>

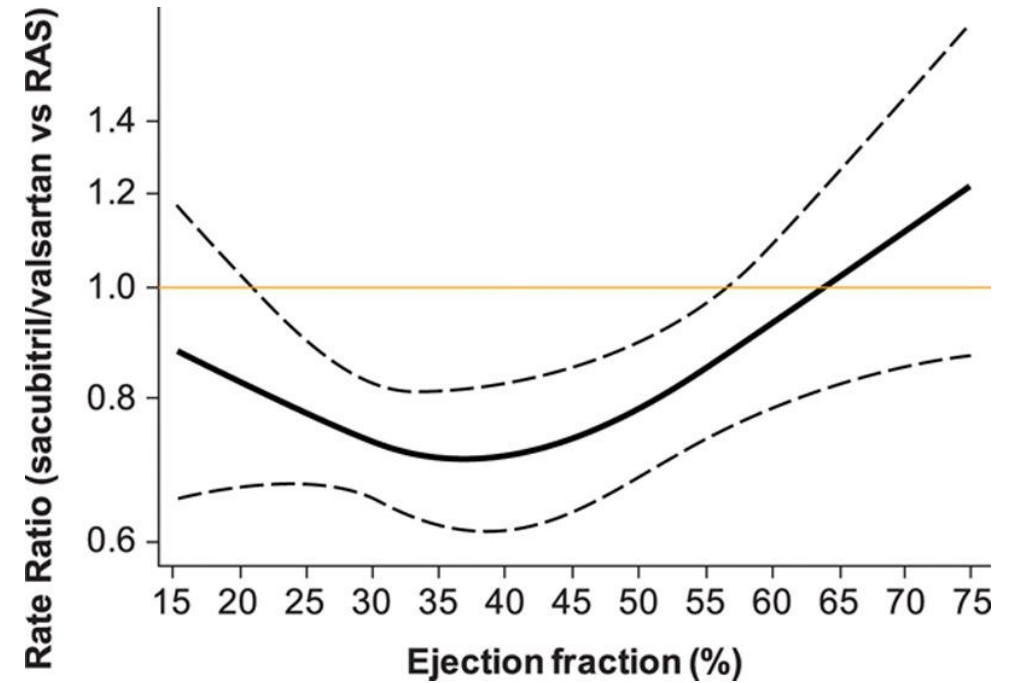
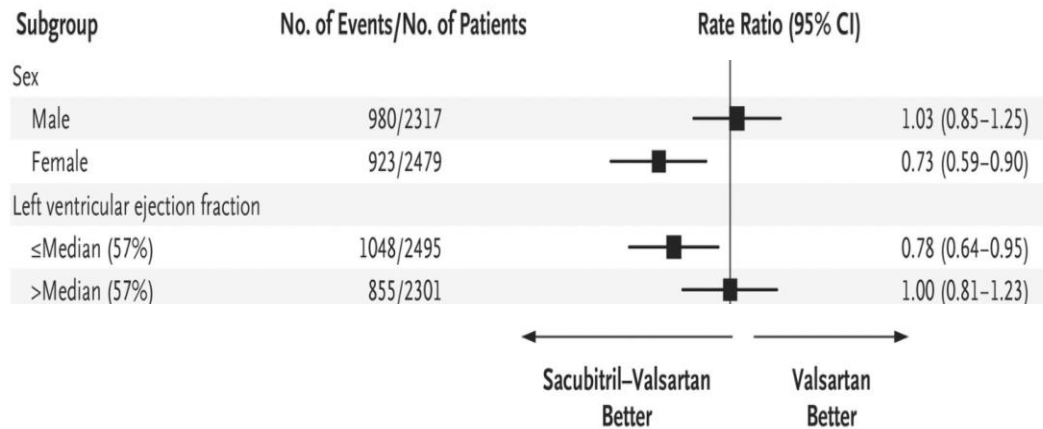


iSGLT2: tractament no específic en tot l'espectre de la IC

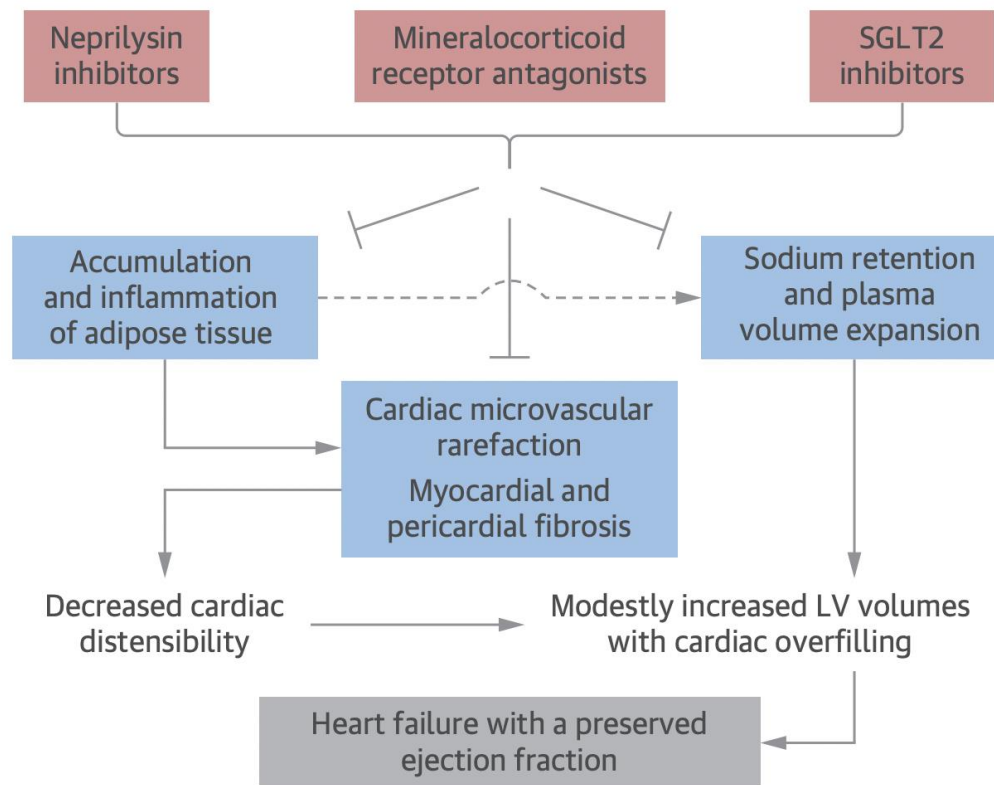


Subgroup No. of Events/No. of Patients Rate Ratio (95% CI)

Tractament segons fenotips: Sacubitril-Valsartan



Tractament segons fenotip: obesitat-IC










Packer, M. et al. J Am Coll Cardiol HF. 2018;6(8):633-9.



- Signes i símptomes de IC
- Augment de presions d'ompliment
- Expansió de volum plasmàtic
- Pèptids baixos
- Poca representació en assajos clínics



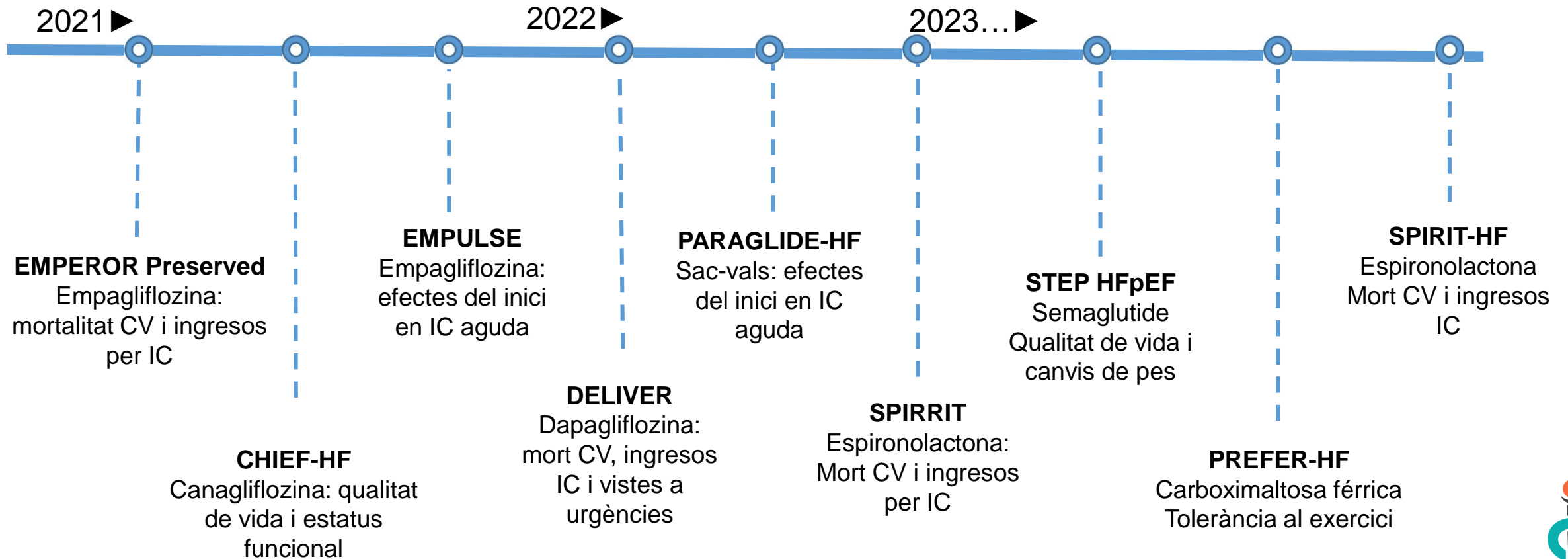
Tractament segons fenotips: ús espironolactona

	LV Geometry	Arterial Stiffness / Pulsatile Arterial Load	Resistive Arterial Load	Mitral Doppler E/e'	Natriuretic Peptides	Other Biomarker Features	Other Clinical Features
P1 	Normal 	↔	↔	↔	↔	<ul style="list-style-type: none"> Higher MMP-9 Higher Syndecan 4 	<ul style="list-style-type: none"> Mild symptoms Smoking Confounded by lung disease? (not genuine HFpEF) Preferential enrollment in Russia/Georgia
P2 	Concentric Remodeling 	↑↑	↑↑	↑	↑↑	<ul style="list-style-type: none"> Osteoprotegerin (calcification) Biomarkers of Innate Immunity / inflammation TIMP-4 	<ul style="list-style-type: none"> CKD Left atrial enlargement AF 
P3 	Concentric Hypertrophy 	↑	↔	↑↑	↑↔	<ul style="list-style-type: none"> Inflammation (TNF-α pathway) Abnormal intermediary metabolism Liver fibrosis (NAFLD?) Renal injury/dysfunction High renin and FAB4 Angiogenesis Mineral metabolism 	<ul style="list-style-type: none"> Favorable response to spironolactone CKD Advanced NYHA class Depression

HR: 0.75
(95% CI: 0.59-0.95)
p 0.016



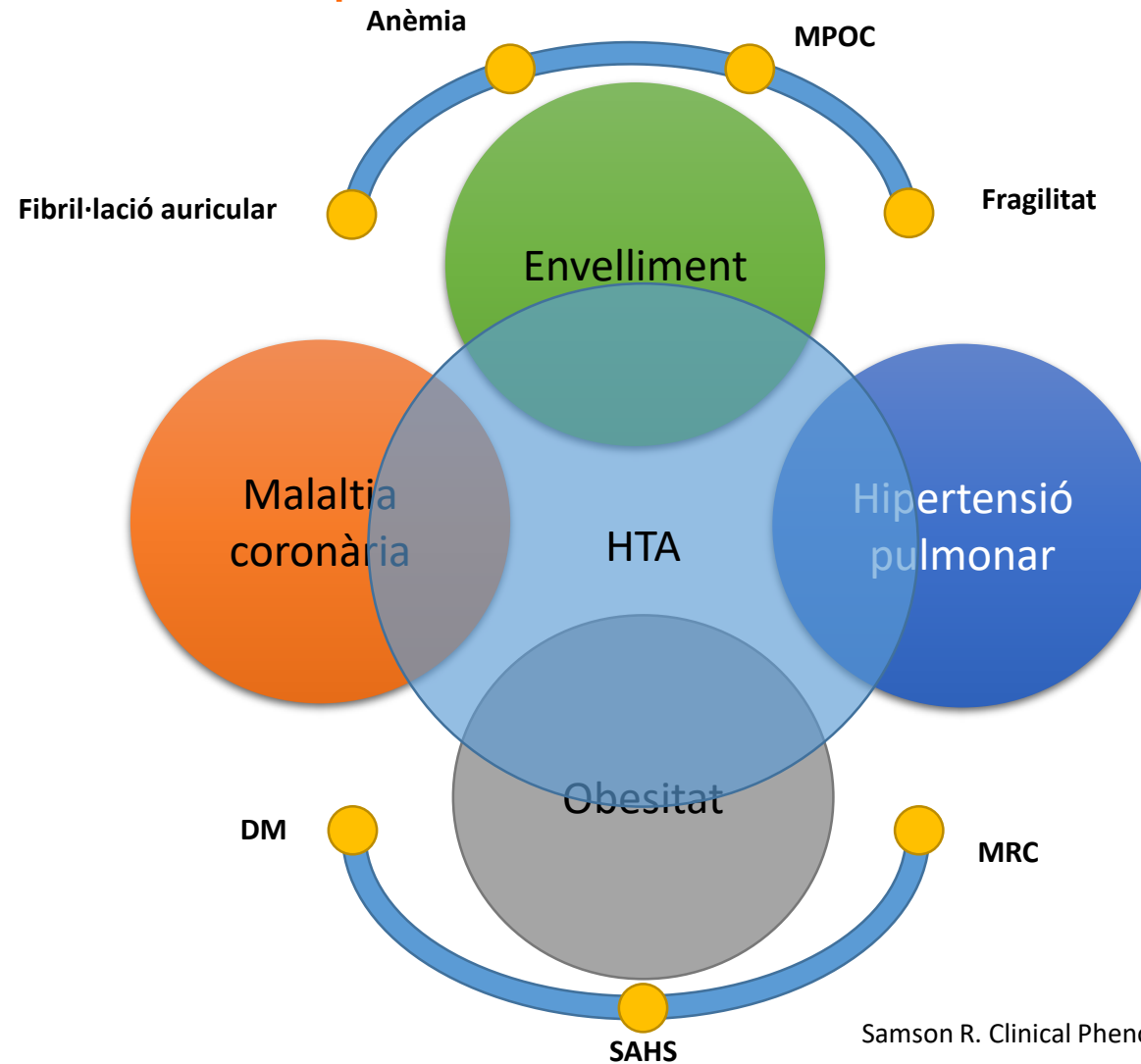
Investigació actual en la IC FEVIp



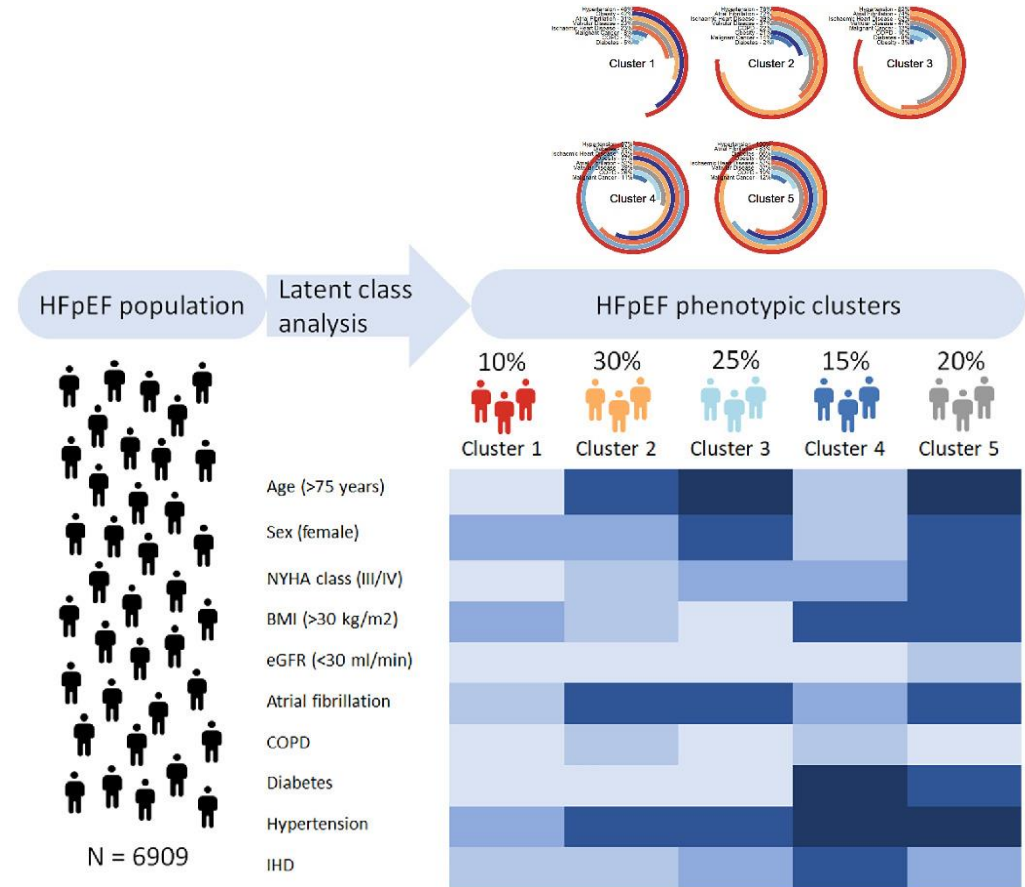
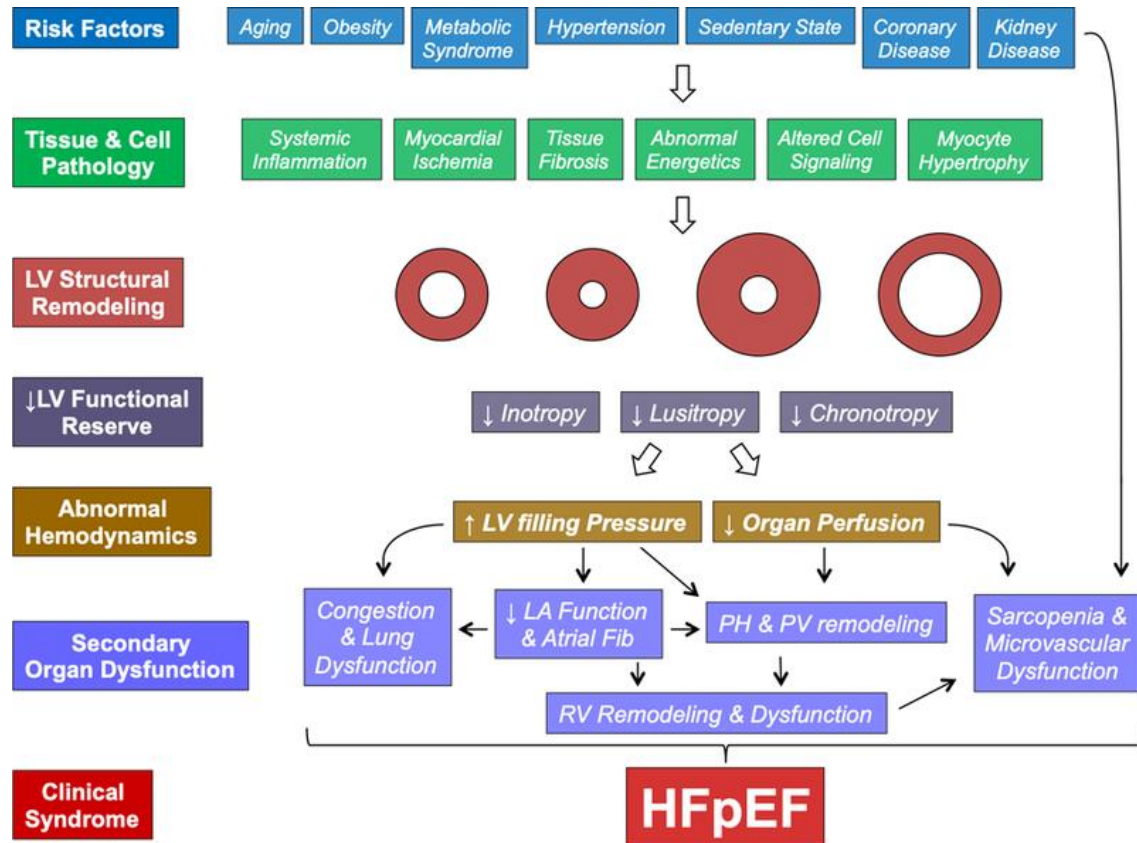
IC amb FEVI preservada: cap a on anem?



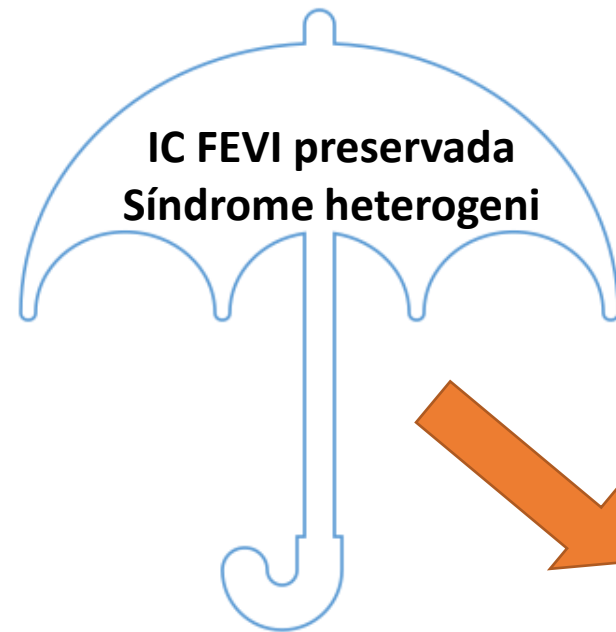
Fenotips en IC amb FEVI preservada



Fenotips en IC amb FEVI preservada: tractament no específic → específic



Fenotips en IC amb FEVI preservada



- FENOTIPAR**
- Biomarcadors
 - Proves d'imatge
 - Biòpsia cardíaca
 - Proves durant exercici
 - "Machine learning"

TRACTAMENT ESPECÍFIC SEGONS FENOTIP

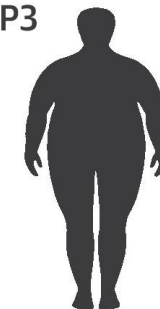
P1



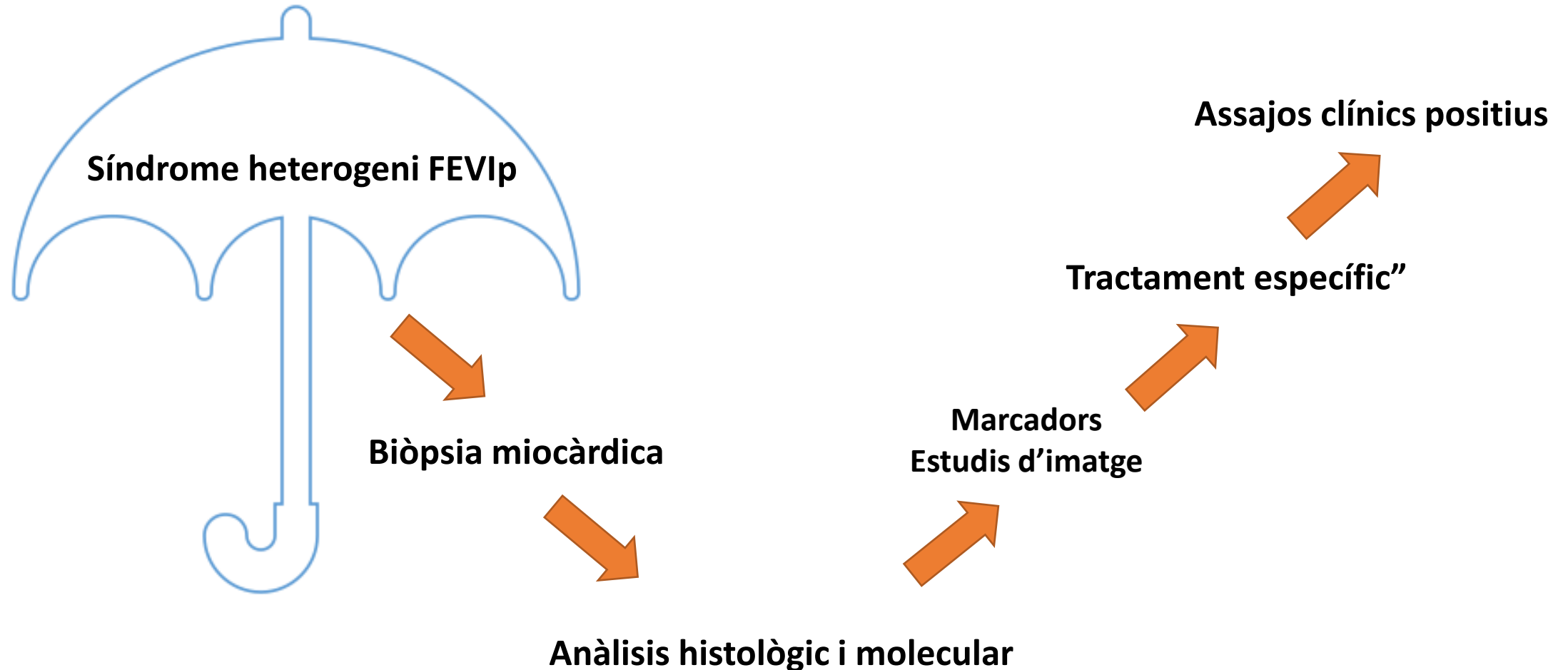
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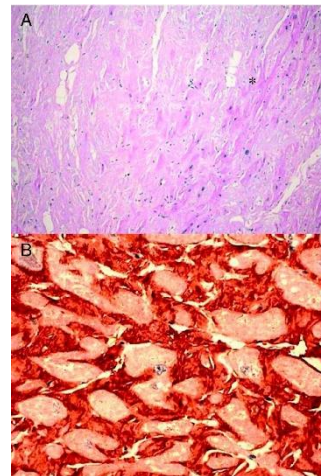
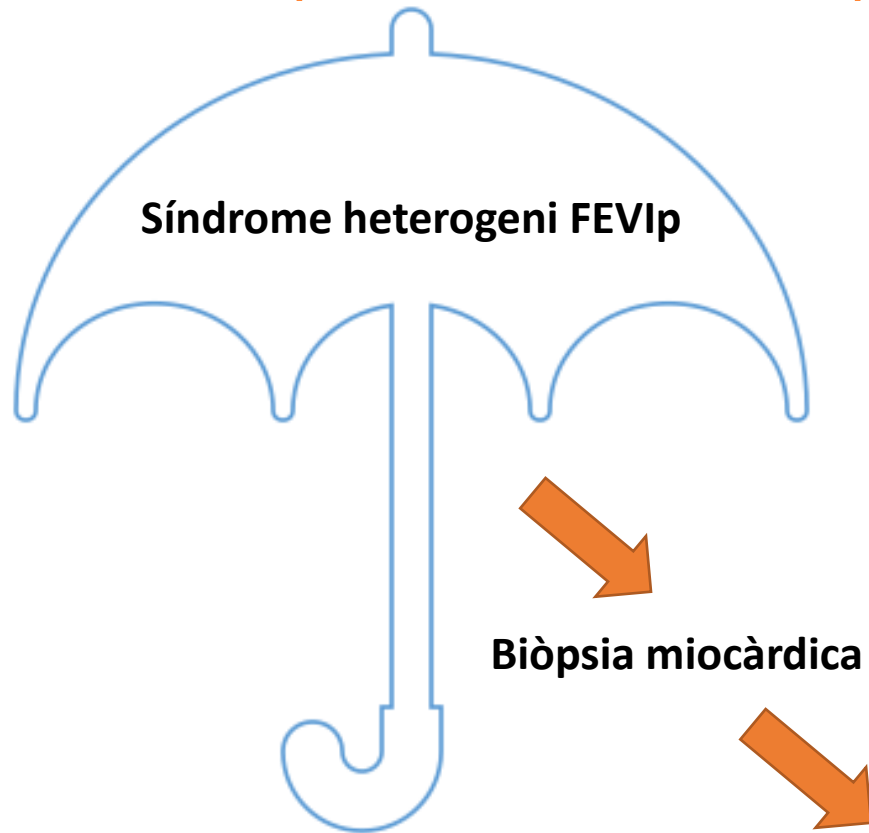
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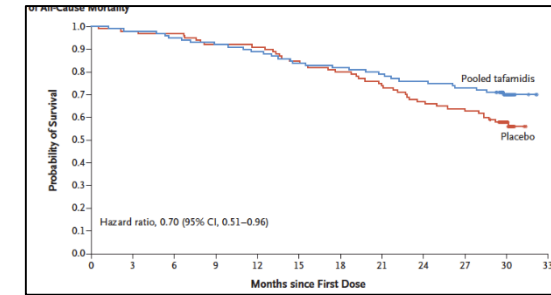
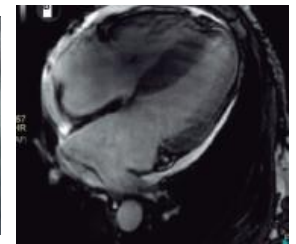
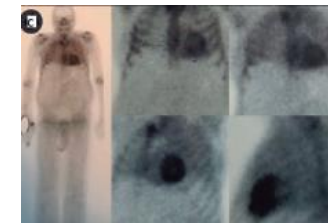
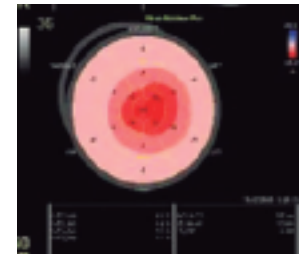
Fenotips en IC amb FEVI preservada



Fenotips en IC amb FEVI preservada: Amiloidosis



Marcadors
Estudis d'imatge



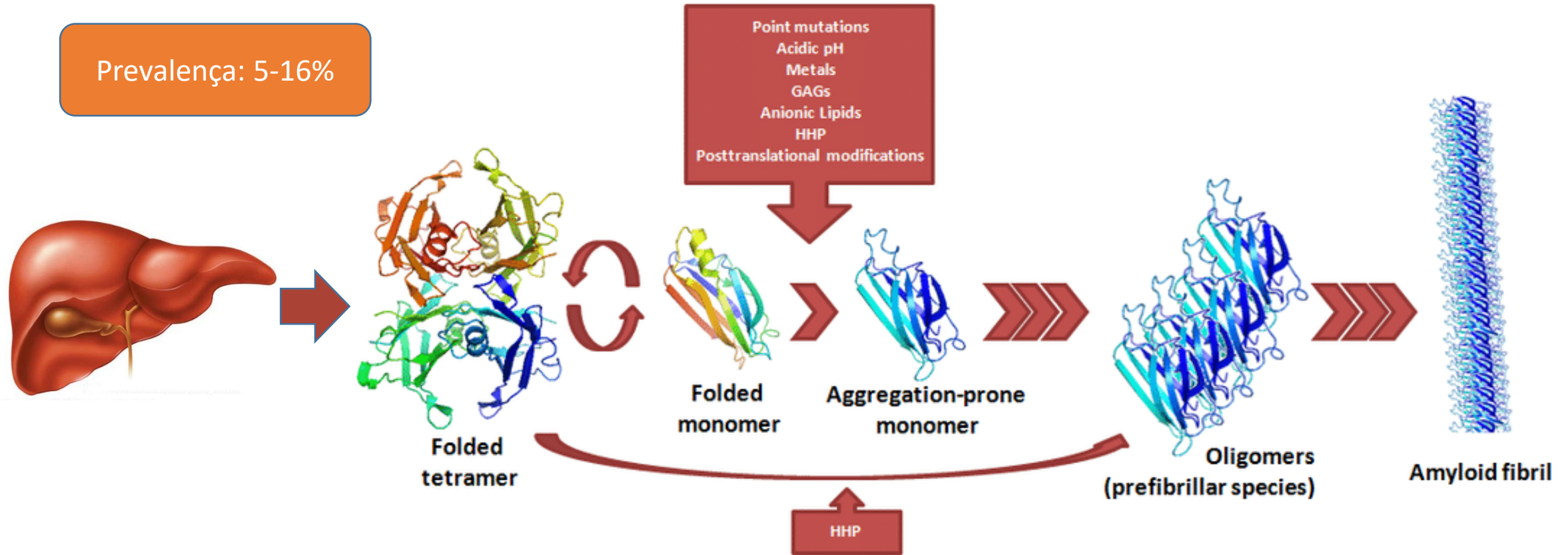
Assajos clínics positius

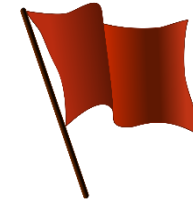
Tafamidis



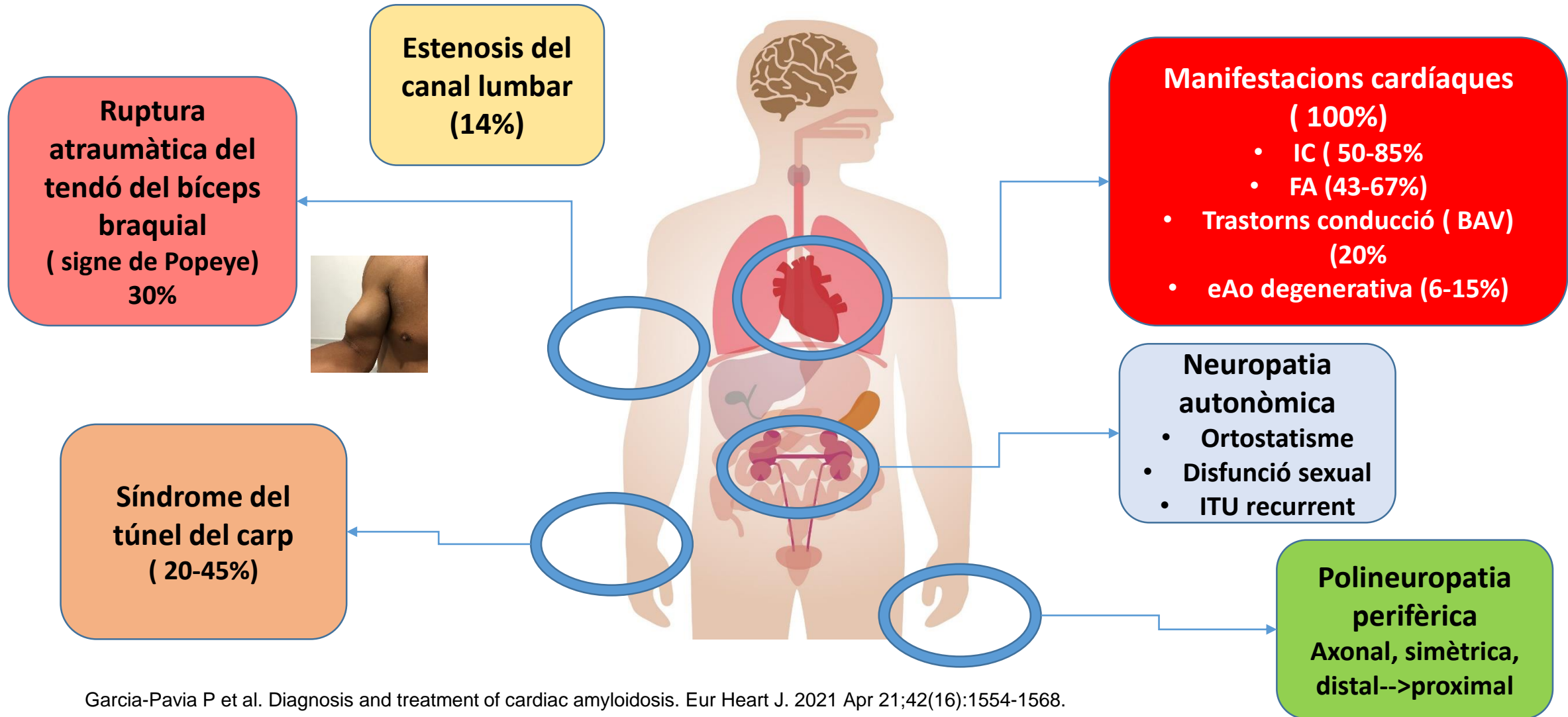
Amiloïdosis cardíaca

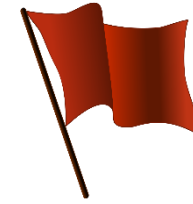
Prevalença: 5-16%





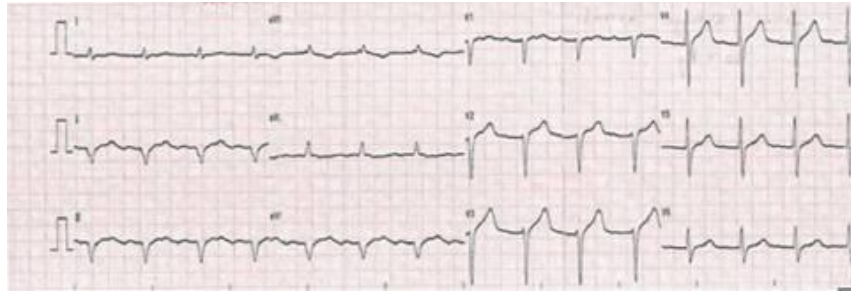
Amiloïdosis cardíaca





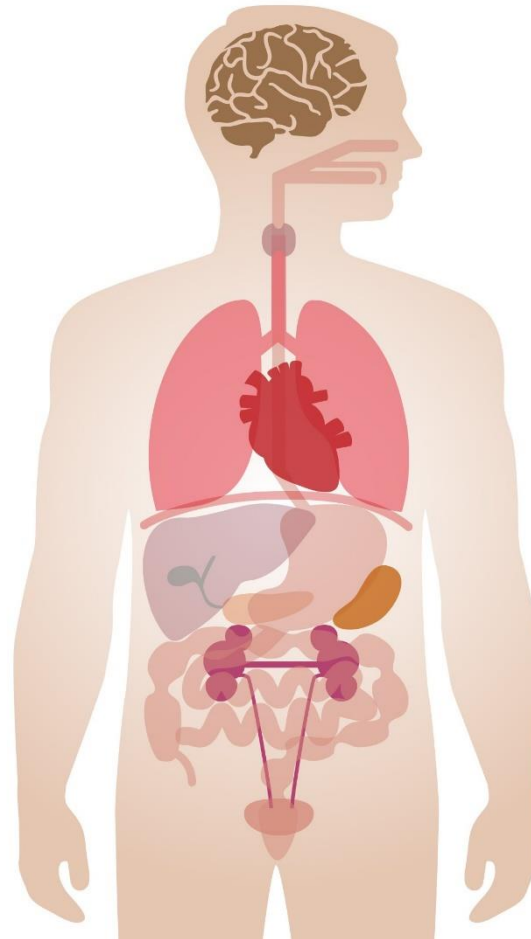
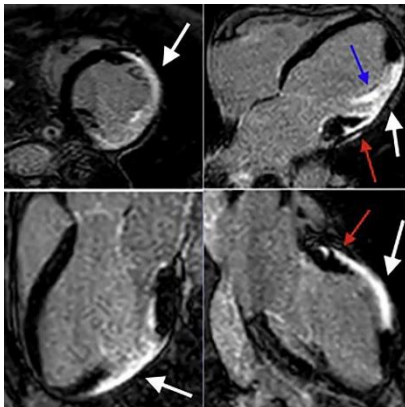
Amiloïdosis cardíaca

Patró de pseudoinfart



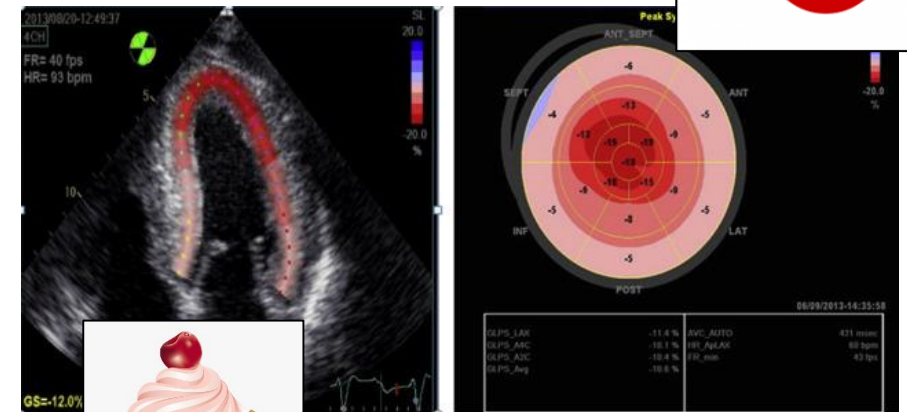
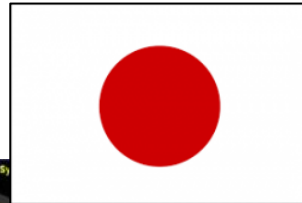
RMN

Patró subendocàrdic global amb realç tardà

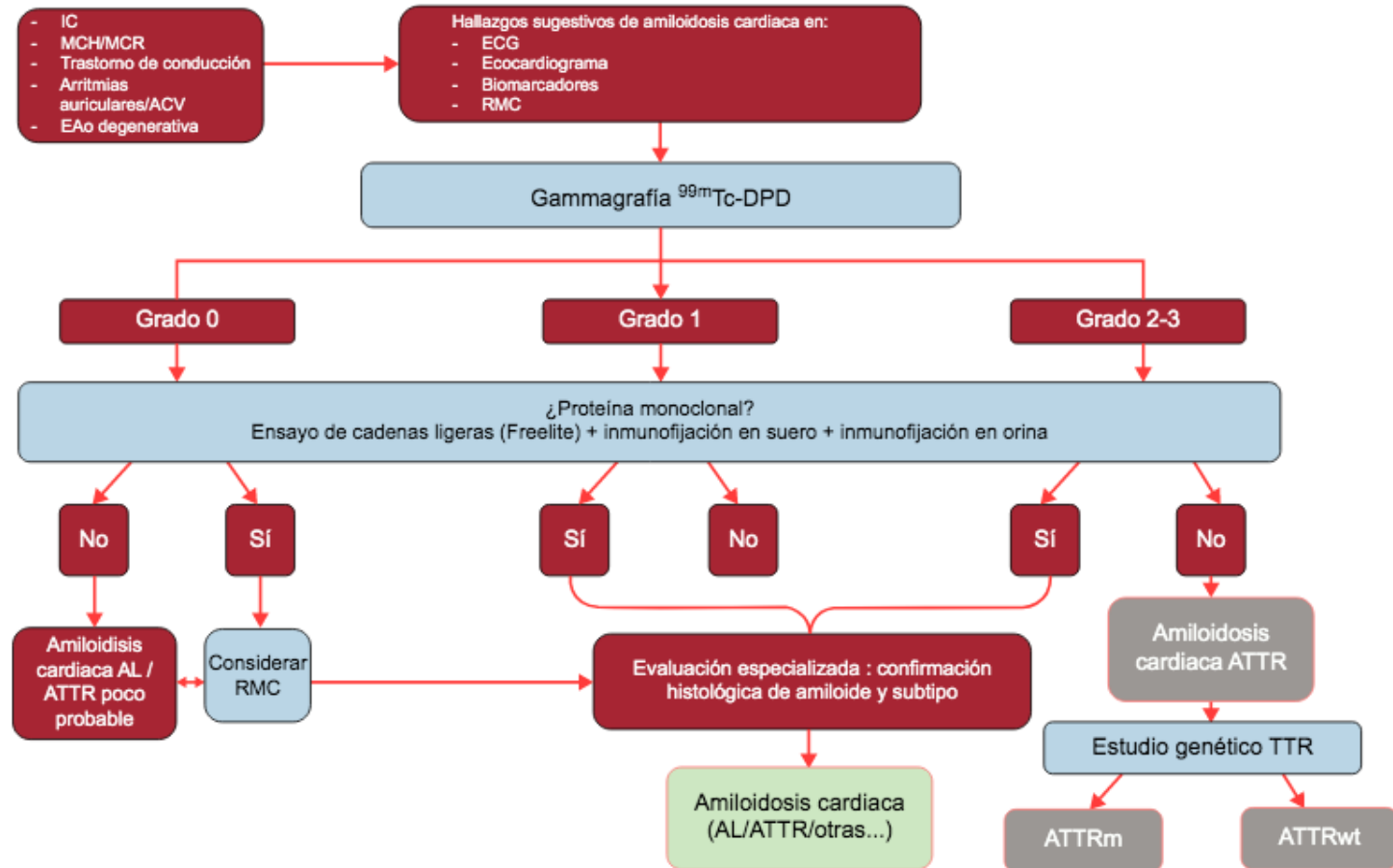
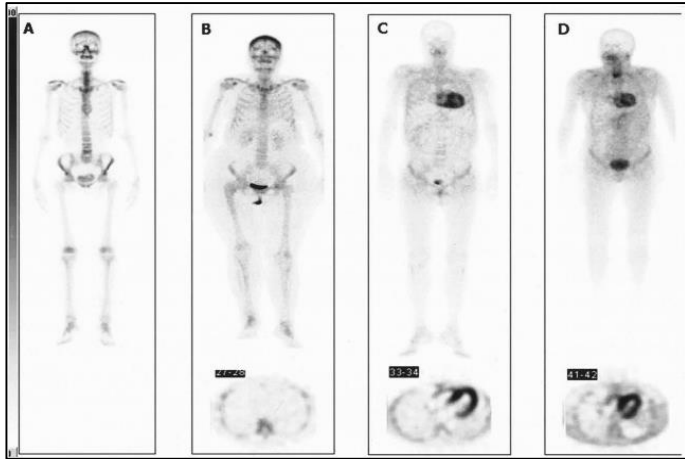


Strain

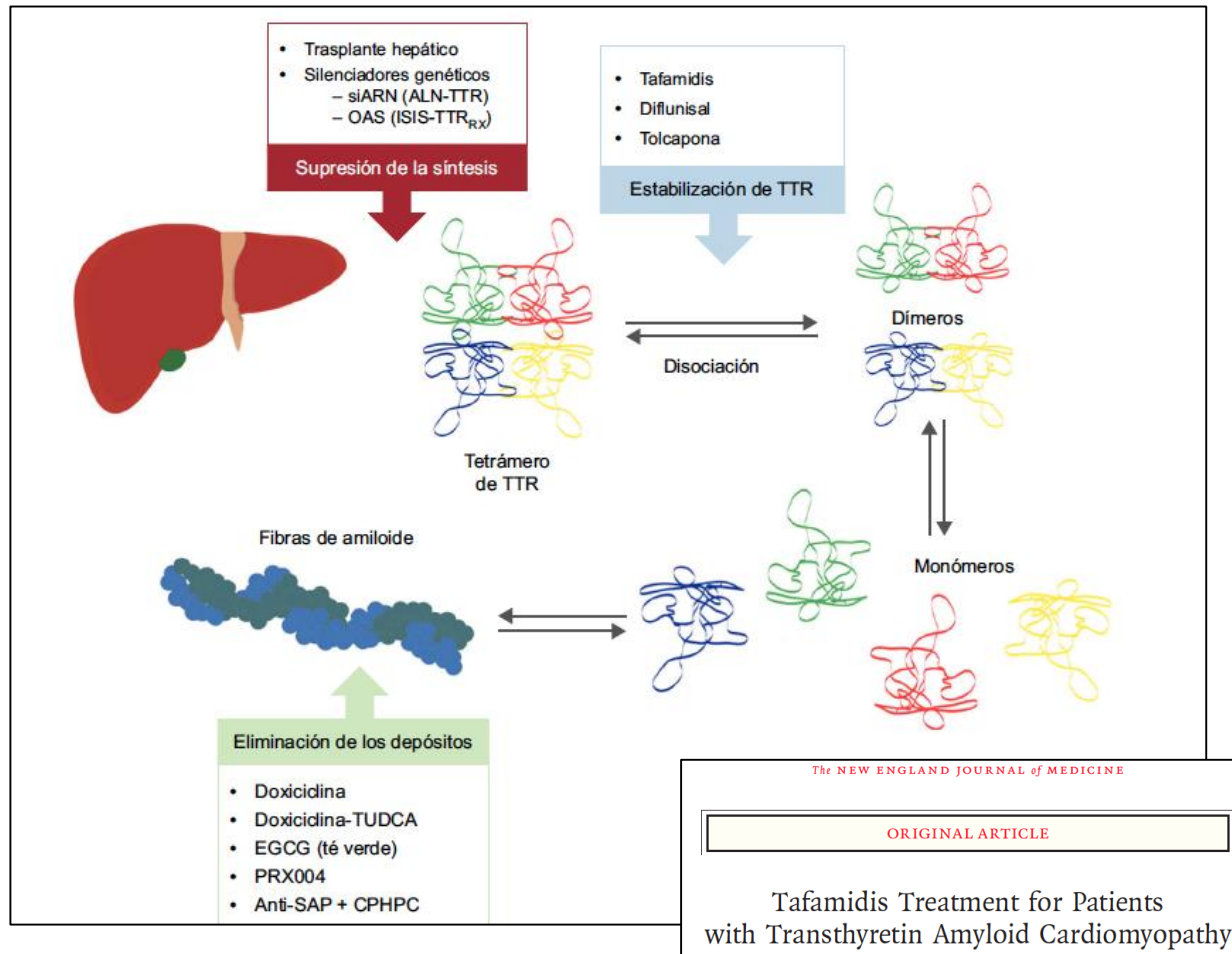
“Apical sparring”, “Bandera de japó” o “Cherry on top pattern”



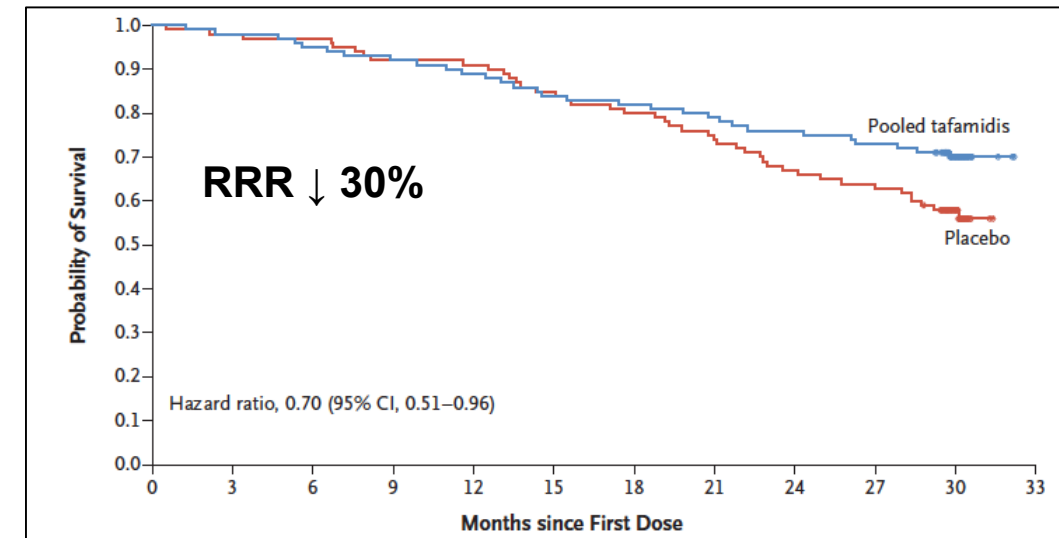
Amiloidosis cardíaca: Diagnòstic



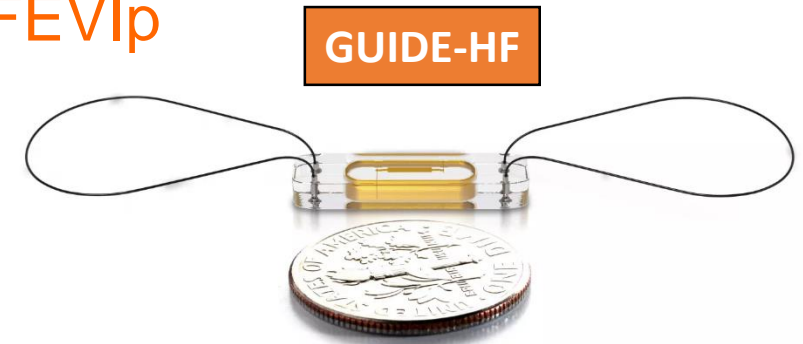
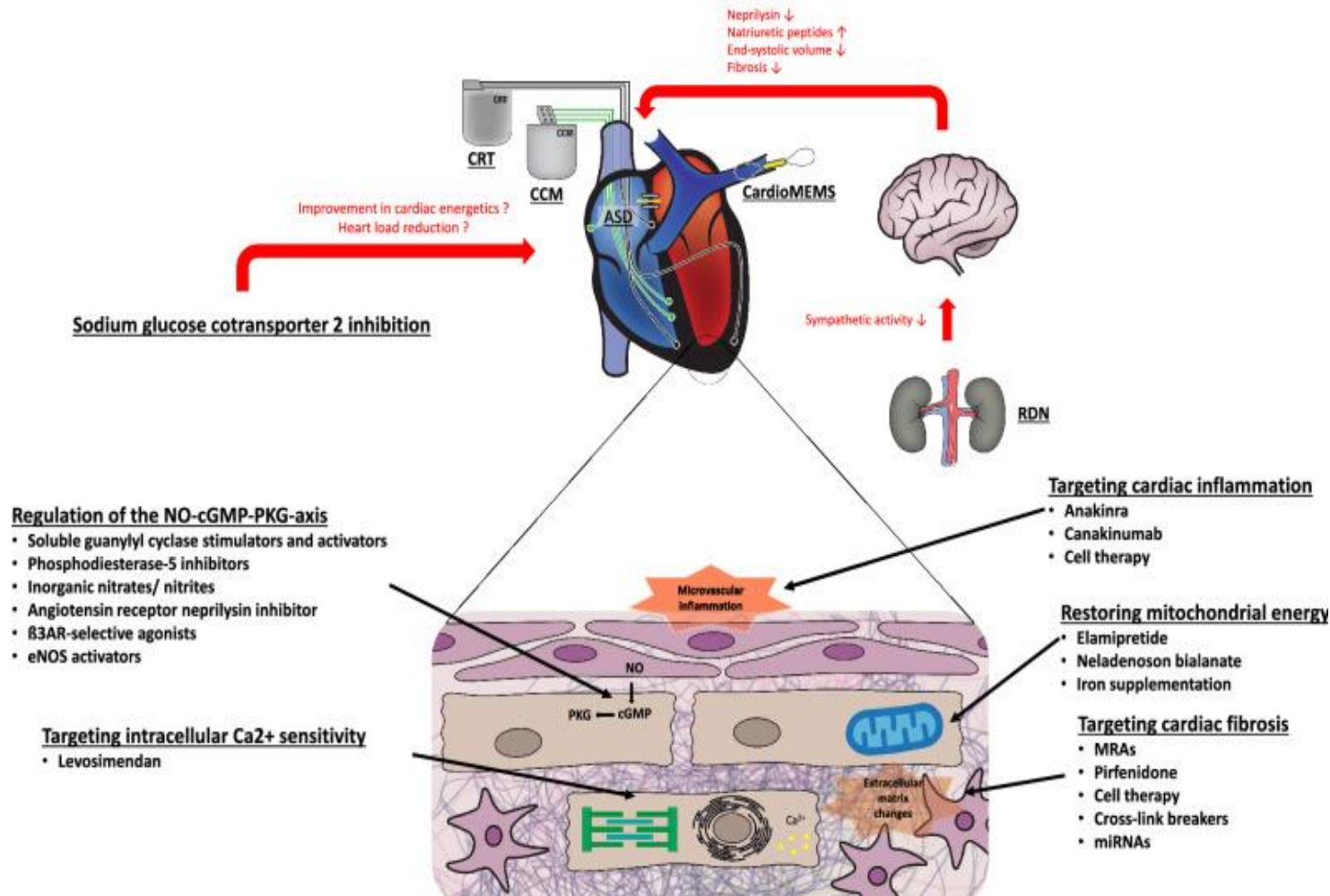
Amiloïdosis cardíaca



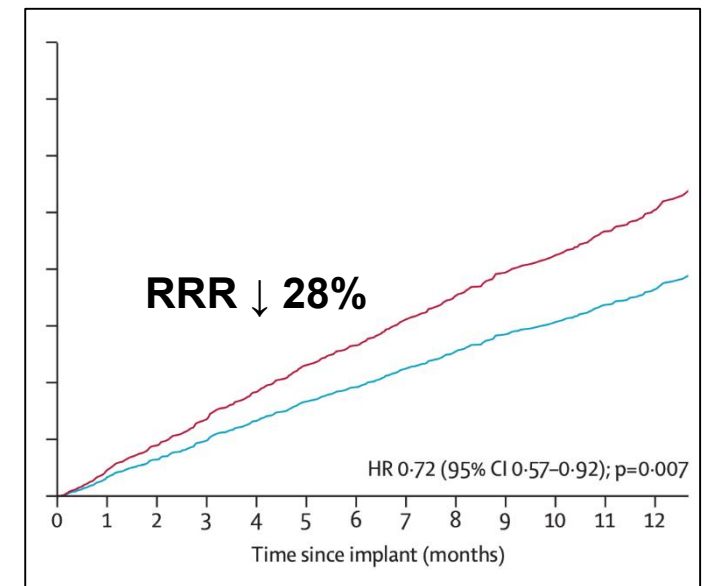
Recommendations	Class ^a	Level ^b
Tafamidis is recommended in patients with genetic testing proven hTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality. ⁹⁷⁹	I	B
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality. ⁹⁷⁹	I	B



Dispositius i tractament en investigació en IC amb FEVIp



GUIDE-HF
Hospitalització per IC
Anàlisi pre-COVID



Conclusions

- La disfunció diastòlica no és sinònim de IC FEVIp
- S'associa a diferents **comorbiditats** que s'han de tractar eficaçment
- **L'afectació multiorgànica** té fins i tot més importància que l'afectació cardíaca
- És una **patologia heterogènia**, pel que és poc probable que un únic tractament millori a tots els pacients
- **Empagliflozina** és el primer fàrmac que ha demostrat benefici: a l'espera de DELIVER per efecte classe.
- La combinació de biomarcadors, proves d'imatge i dades clíniques en ajuden a establir **fenotips**
- **Amiloïdosis** com a entitat emergent
- Es necessita afegir pacients fenotipats en els assajos clínics

