The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

Encountering Heart Failure Patients with Frailty

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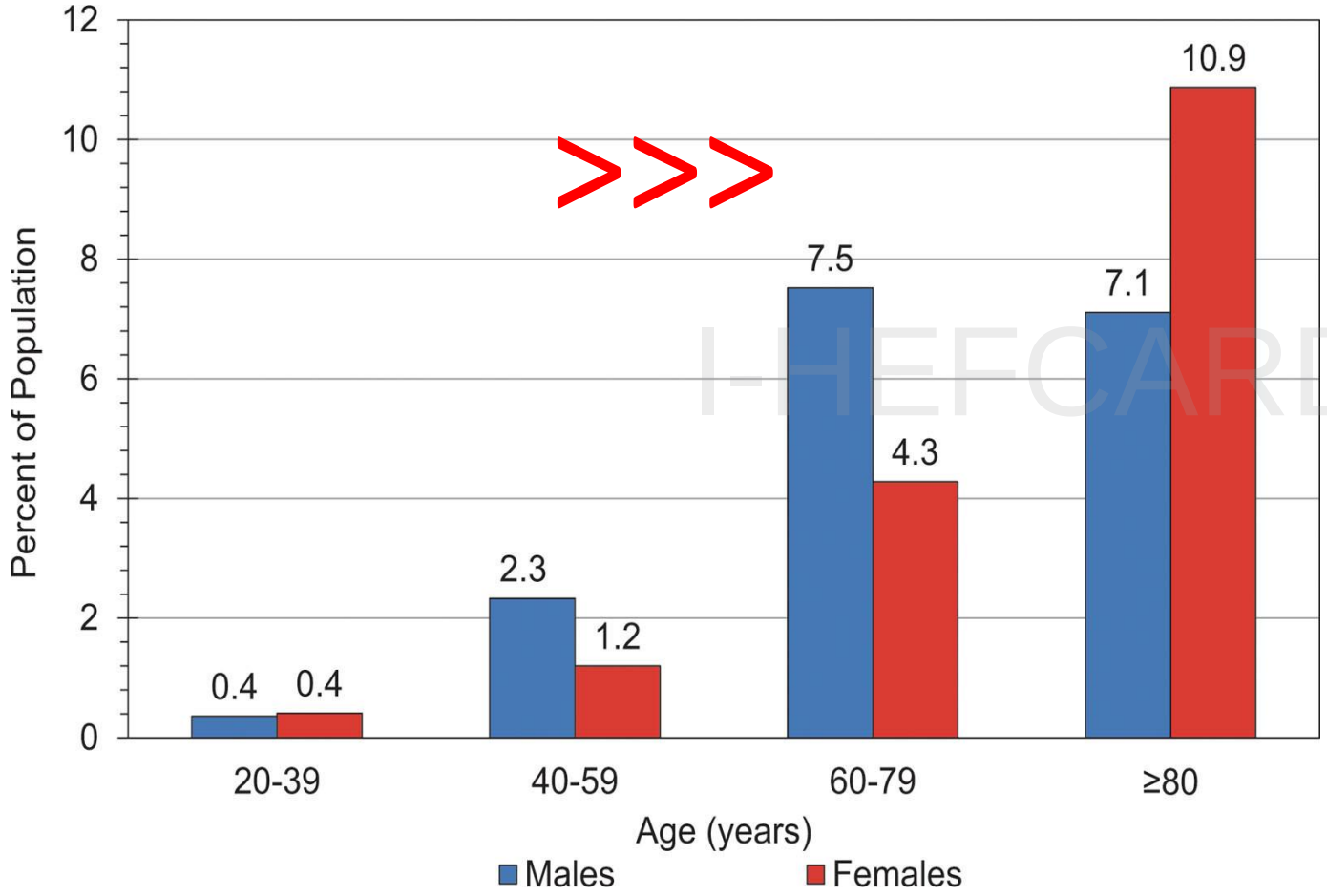
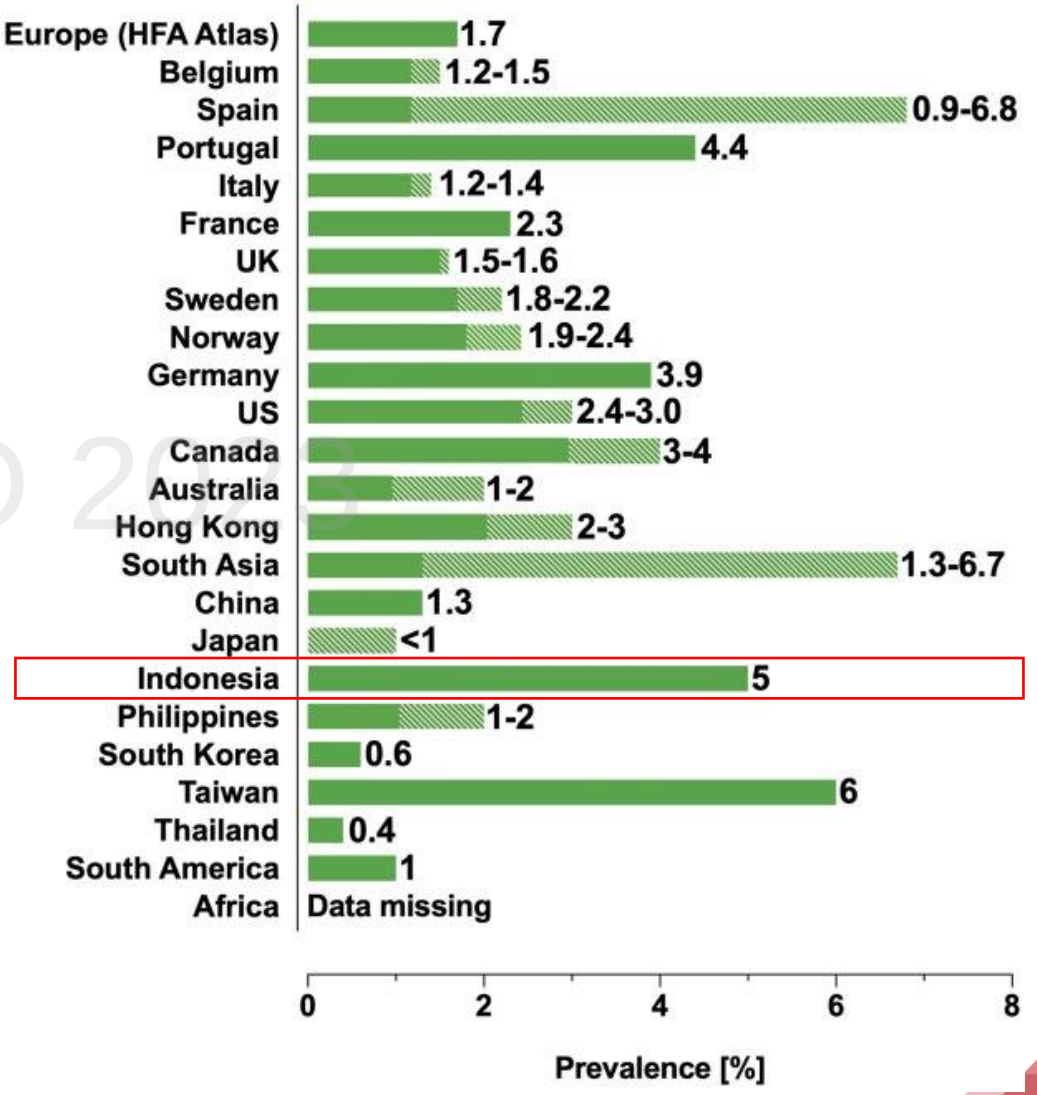
Epidemiology of Heart Failure: Lifetime Risk and Projected Rise in The Incidence and Prevalence





Savarese G et al. Cardiovascular Research. 2022
Tsao CW et al. Circulation. 2023
American Heart Association editorial staff. 2017

The goals of treatment in patients with HF

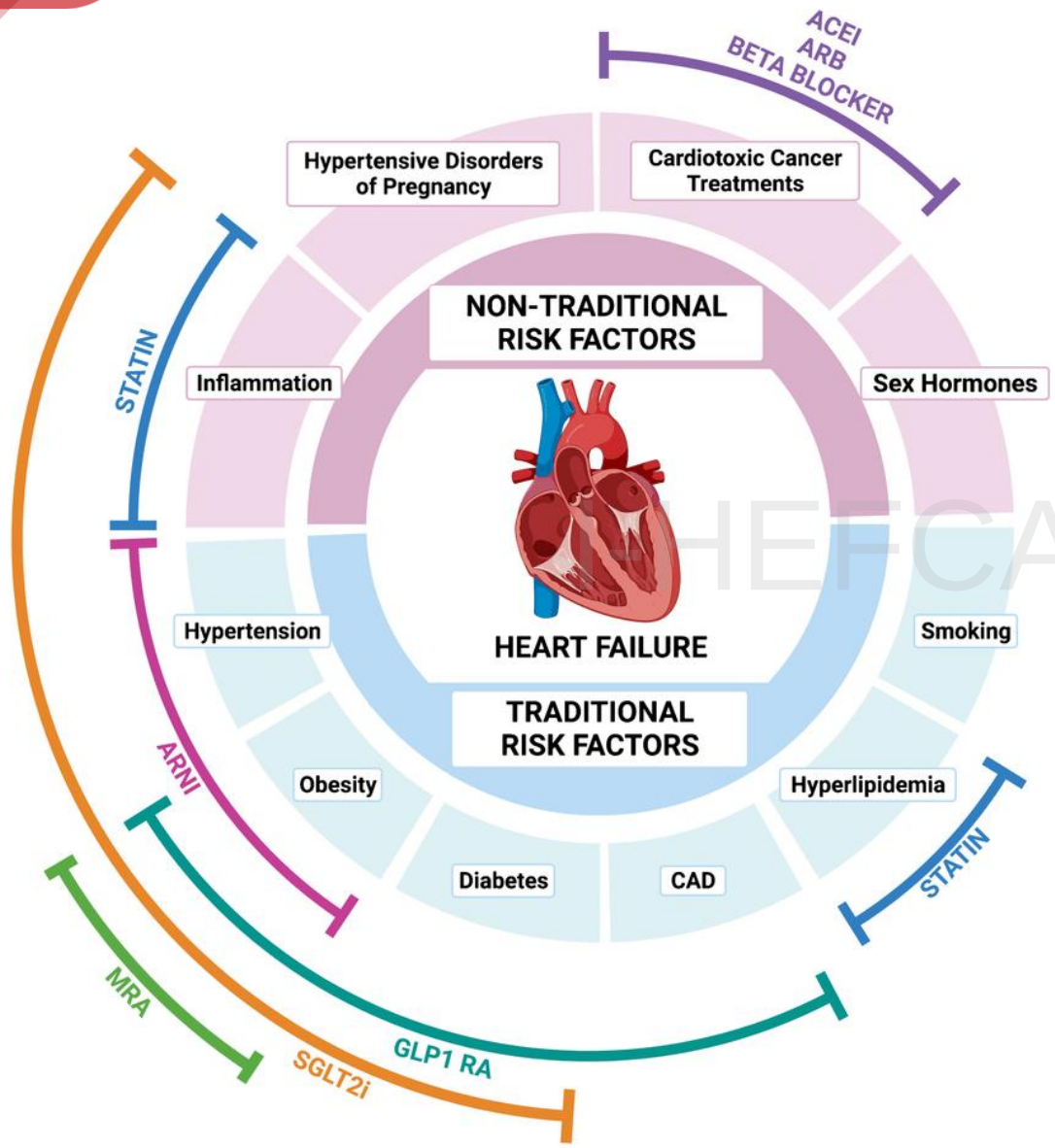
To make patients feel better

To prevent disease progression

To make patients live longer

Mc.Donagh et al. Eur Heart J. 2021

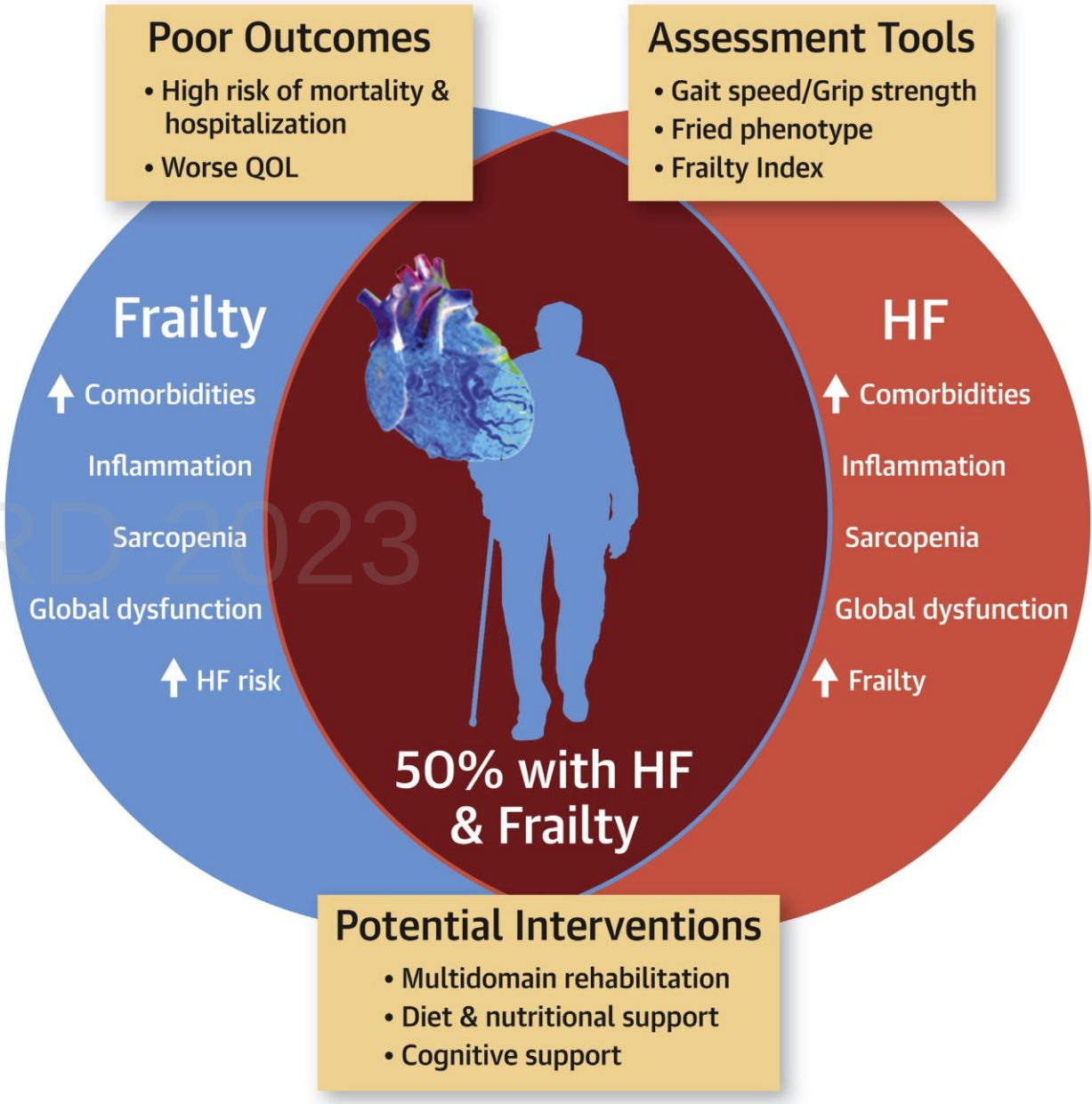
Risk Factors of Heart Failure



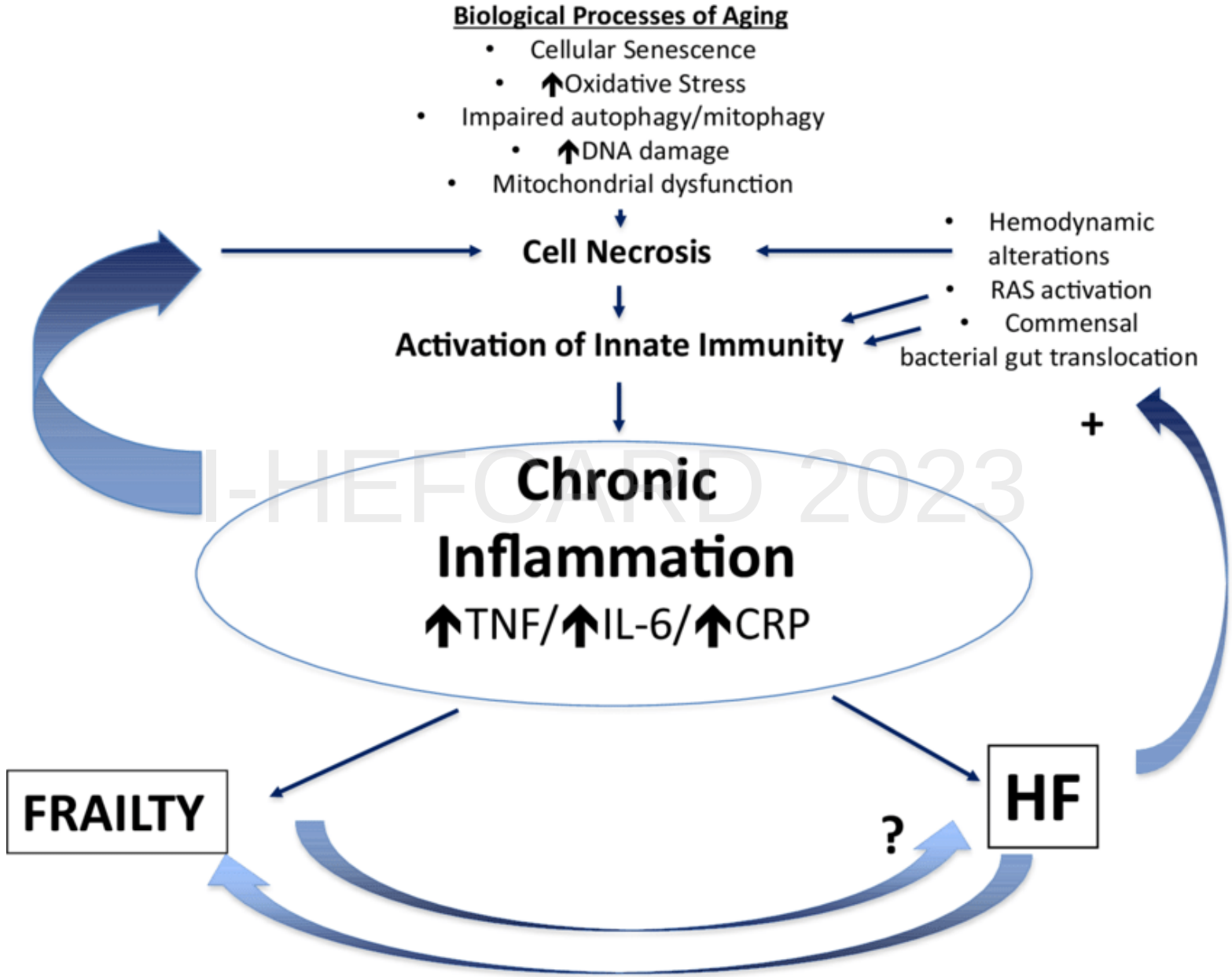
Everitt IK et al. Current atherosclerosis reports. 2022

Elderly Patients with HF

- In patients with HF, age is associated with frailty; leading to increased risk of cardiovascular events and mortality during short and long term follow-up
  - The imbalance between the anabolic and catabolic state in HF → accelerate frailty.
  - Up to 79% HF patients are frail and up to 6x more likely to be frail than the general population
- Elderly patients with HF often present with complex comorbidities and poly-pharmacy
- The clinical decision-making process required in these patients may be very challenging

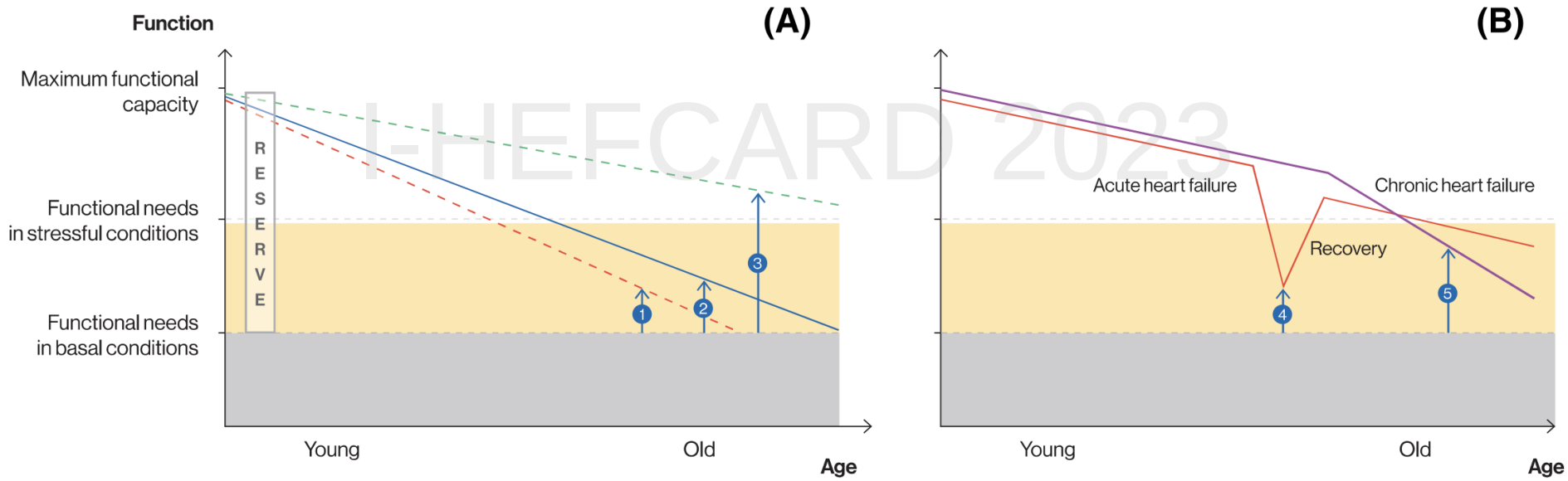


[1]Butt JH et al. Journal of American College of Cardiology. 2022
[2]Vitale C, et al. Cardiac failure review. 2018
Pandey, A. et al. J Am Coll Cardiol HF. 2019



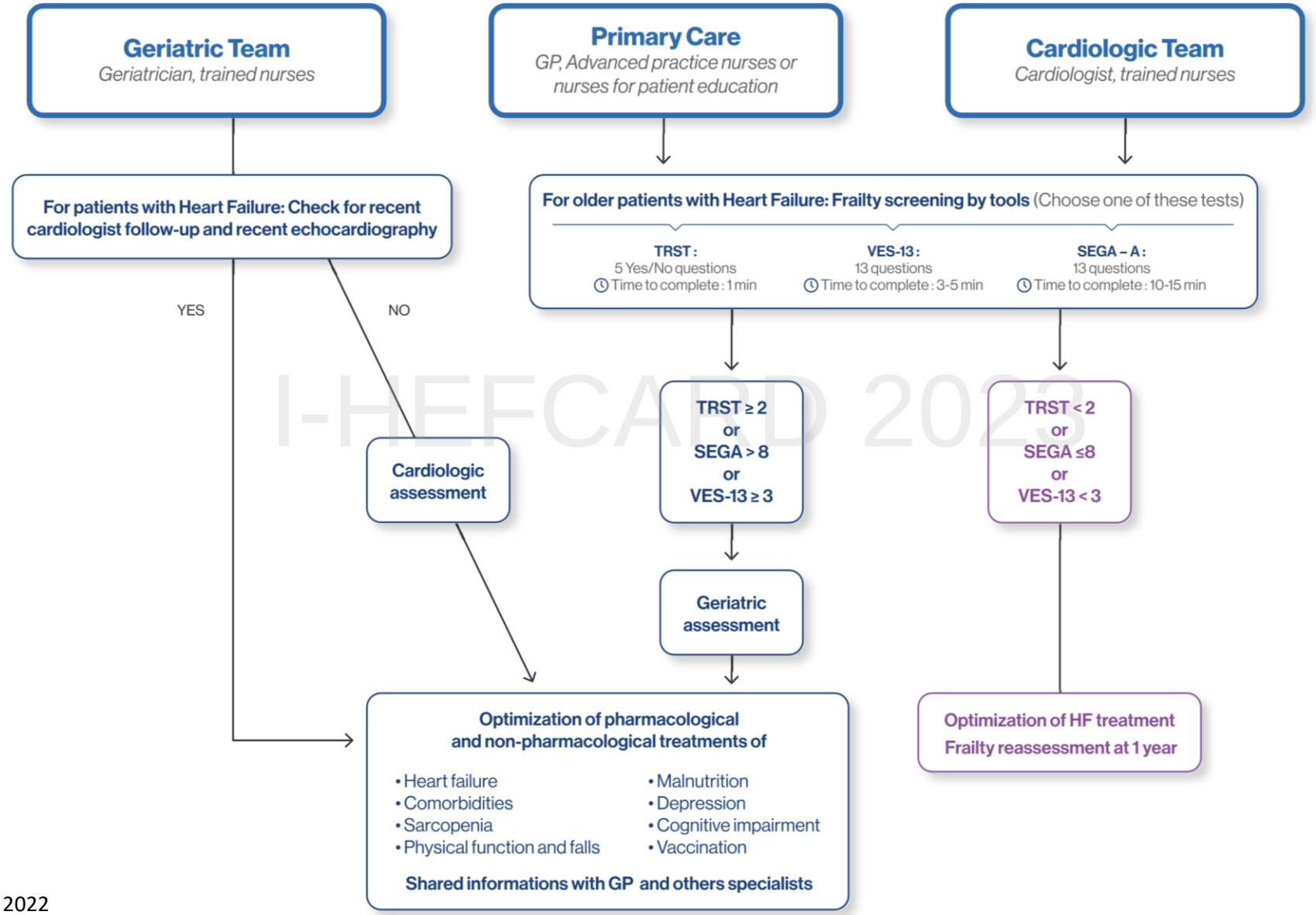
Bellumkonda L, et al. Pathophysiology of heart failure and frailty: a common inflammatory origin?.Aging cell. 2017

Figure 1 (A) Schematic mechanisms of frailty in aging. Maximum functional capacity (blue line) decreases with age, as well as functional reserve. Frailty occurs when maximum functional capacity decreases below the level required under stressful conditions (arrow 2). In young individuals, functional capacity is sufficient to overcome stressful conditions. The slope of functional decline varies among individuals. Persons with slower decline experience successful aging and are not frail (green line, arrow 3) and those with steeper decline experience accelerated aging and greater frailty (red line and arrow 1). (B) Heart failure (HF) may alter functional capacity through a decrease functional reserve and an increase frailty (arrows 4 and 5). The effects of acute HF on frailty might be reversible after recovery.



Boureau et al. ESC Heart failure. 2022

Figure 2 Collaborative care for older patients with HF.



Boureau et al. ESC Heart failure. 2022

Table 2 Details and predictive values of frailty screening tools: TRST, SEGA-A, and VES-13

	SEGA A	VES-13	TRST
Type of instrument	Patient assessment	Questionnaire for patients or caregivers (face-to-face or telephone interview)	Patient assessment
Duration (min)	10	3–5	1–5
Number of items	13	13	5
Type of items	Age Drugs Mood Self-perception of health Falls Nutritional status Co-morbidities Incontinence Need of help for daily living activities Cognitive function	Age Self-perception of health Difficulties for 6 physical activities Limitation for 5 activities of daily living due to health problems	History or evidence of cognitive impairment Recent hospitalization or emergency visit Gait disturbances or falls Use of 5 drugs or more Independence for activities of daily living performed by a nurse, elder abuse, substance abuse, medication non-compliance
Items Scoring and Scale Threshold	Three-level Threshold > 8	Two to three-level Threshold ≥ 3	Two-level Threshold ≥ 2
Context of care of validation	Emergency, hospitalization	Community dwelling elders in primary care, hospitalization, surgery and cancer patients, emergency, inpatients of cardiology ward*	Emergency, hospitalization
Predictive values (Se, Spe) for			
Mortality	Yes[45]	Yes (Se: 87%, Sp: 47%)[42]	Yes
Institutionalization	Yes	Yes (Se: 92%, Sp: 50%)[42]	No
Hospitalization	Yes	No	Yes (Se: 83%, Sp: 32%)[48]
Functional decline	Yes	Yes (Se: 91%, Sp: 59%)[42]	Yes (Se: 66%, Sp: 47%)[48]
Strengths	Multiple predictive outcomes	Validated in numerous different settings Rapid screening tool	Simple 5 questions Short screening tool
Limitations	Require a longer time to complete	Sensitivity and specificity are unknown to predict risk of hospitalization	Sensitivity and specificity are unknown to predict risk of institutionalization

TRST, Triage Risk Screening Tool; SEGA, Short Emergency Geriatric Assessment); VES13, Vulnerable Elders Survey-13; Se, Sensitivity; Spe, Specificity.

Boureau et al. ESC Heart failure. 2022

TABLE 4 Baseline Characteristics of Frail Vs. Non-Frail HF Patients Categorized According to Different Frailty Assessment Tools

	Frailty Assessment in Patients With HF (n = 467)									
	Fried			DI			EFS			
	Non-Frail (n = 223)	Frail (n = 244)	p Value	Non-Frail (n = 302)	Frail (n = 165)	p Value	Non-Frail (n = 327)	Frail (n = 140)	p Value	Missing
Demographics										
Age, yrs	72 (64-78)	80 (74-84)	<0.001	74 (66-80)	80 (74-85)	<0.001	74 (66-80)	80 (75-85)	<0.001	0
Male	165 (74)	148 (61)	0.002	214 (71)	99 (60)	0.02	224 (69)	89 (64)	0.30	0
HR, beats/min	70 (61-77)	71 (60-82)	0.14	70 (60-80)	70 (62-82)	0.80	70 (60-79)	70 (61-83)	0.21	0
BP systolic, mm Hg	140 (125-157)	138 (126-166)	0.17	140 (125-158)	137 (128-167)	0.15	141 (126-162)	137 (125-162)	0.79	0
BP diastolic, mm Hg	74 (67-83)	75 (65-83)	0.35	75 (67-83)	74 (65-83)	0.43	75 (67-83)	73 (64-82)	0.02	0
NYHA functional class III/IV	18 (8)	85 (35)	<0.001	40 (13)	63 (38)	<0.001	44 (14)	59 (42)	<0.001	0
HFrEF	153 (69)	138 (57)	0.007	201 (67)	90 (54)	0.10	212 (65)	79 (56)	0.09	0
HFnEF	70 (31)	106 (43)		101 (33)	75 (46)		115 (35)	61 (44)		
Height, m	1.70 (1.64-1.76)	1.66 (1.59-1.74)	<0.001	1.70 (1.63-1.75)	1.65 (1.59-1.74)	0.001	1.69 (1.62-1.75)	1.65 (1.59-1.74)	0.003	0
Weight, kg	86 (74-102)	79 (66-96)	0.006	84 (72-99)	78 (66-97)	0.05	84 (72-99)	78 (64-97)	0.003	0
BMI, kg/m^2	29.4 (26.0-33.3)	28.7 (24.4-32.8)	0.15	29.1 (25.6-33.2)	28.8 (24.3-33.1)	0.52	29.1 (25.8-33.3)	28.6 (23.6-32.7)	0.07	0
Comorbidities										
Charlson score	7 (5-9)	9 (8-11)	<0.001	7 (5-9)	10 (9-12)	<0.001	8 (6-9)	10 (8-12)	<0.001	0
MI	98 (44)	100 (41)	0.52	121 (40)	77 (47)	0.17	142 (43)	56 (40)	0.49	0
PVD	28 (13)	44 (18)	0.10	34 (11)	38 (23)	0.001	42 (13)	30 (21)	0.02	0
HTN	139 (62)	174 (71)	0.04	192 (64)	121 (73)	0.03	221 (68)	92 (66)	0.69	0
CVA/TIA	22 (10)	49 (20)	0.002	26 (9)	45 (27)	<0.001	37 (11)	34 (24)	<0.001	0
Diabetes	69 (31)	94 (39)	0.05	90 (30)	73 (44)	0.002	106 (33)	57 (41)	0.21	0
Dementia	4 (2)	44 (18)	<0.001	8 (3)	40 (24)	<0.001	5 (2)	43 (31)	<0.001	0
COPD	47 (21)	93 (38)	<0.001	73 (24)	67 (41)	<0.001	78 (24)	62 (44)	<0.001	0
Depression	28 (13)	65 (27)	<0.001	42 (14)	51 (31)	<0.001	48 (15)	45 (32)	<0.001	0
Anemia	77 (35)	141 (58)	<0.001	110 (36)	108 (66)	<0.001	126 (39)	92 (66)	<0.001	0
Recurrent falls	32 (14)	141 (58)	<0.001	63 (21)	110 (67)	<0.001	83 (25)	90 (64)	<0.001	0
Incontinence	8 (4)	25 (10)	0.005	11 (4)	22 (13)	0.001	13 (4)	20 (14)	<0.001	0

TABLE 3 Prevalence of Frailty in Different Subgroups of Patients With CHF

	Frailty					
	Assessment Tools				Screening Tools	
	Fried (n = 250)	DI (n = 165)	EFS (n = 142)	CFS (n = 209)	AFN (n = 230)	DFI (n = 230)
Heart rhythm						
SR (n = 252)	46 (116)	32 (80)	25 (64)	39 (98)	40 (100)	43 (108)
AF (n = 215)	60 (128)	40 (85)	35 (76)	50 (108)	54 (117)	54 (116)
p value (SR vs. AF)	0.004	0.02	0.02	0.02	0.001	0.02
BMI categories, kg/m^2						
<24.9 (n = 111)	60 (67)	41 (46)	41 (46)	53 (59)	62 (69)	64 (71)
25.0-29.9 (n = 158)	50 (79)	30 (48)	25 (39)	42 (66)	45 (71)	54 (86)
≥30 (n = 198)	50 (98)	36 (71)	28 (55)	41 (81)	39 (77)	34 (67)
p value (BMI categories)	0.15	0.17	0.009	0.09	<0.001	<0.001
HF phenotype						
HFrEF (n = 291)	47 (138)	31 (90)	27 (79)	40 (117)	39 (114)	42 (122)
HFnEF (n = 176)	60 (106)	43 (75)	35 (61)	51 (89)	59 (103)	58 (102)
p value (HFrEF vs. HFnEF)	0.007	0.01	0.09	0.03	<0.001	0.001
NYHA functional class						
I/II (n = 364)	44 (159)	28 (102)	22 (81)	35 (128)	40 (145)	42 (154)
III/IV (n = 103)	83 (85)	61 (63)	57 (59)	76 (78)	70 (72)	68 (70)
p value (I/II vs. III/IV)			<0.001			
NT-proBNP, ng/l						
<1,000 (n = 215)	41 (88)	26 (56)	22 (47)	33 (70)	32 (68)	35 (76)
1,000-2,000 (n = 108)	55 (59)	35 (38)	30 (32)	45 (49)	52 (56)	54 (58)
>2,000 (n = 144)	67 (97)	49 (71)	42 (61)	60 (87)	65 (93)	63 (90)
p value (NT-proBNP categories)			<0.001			

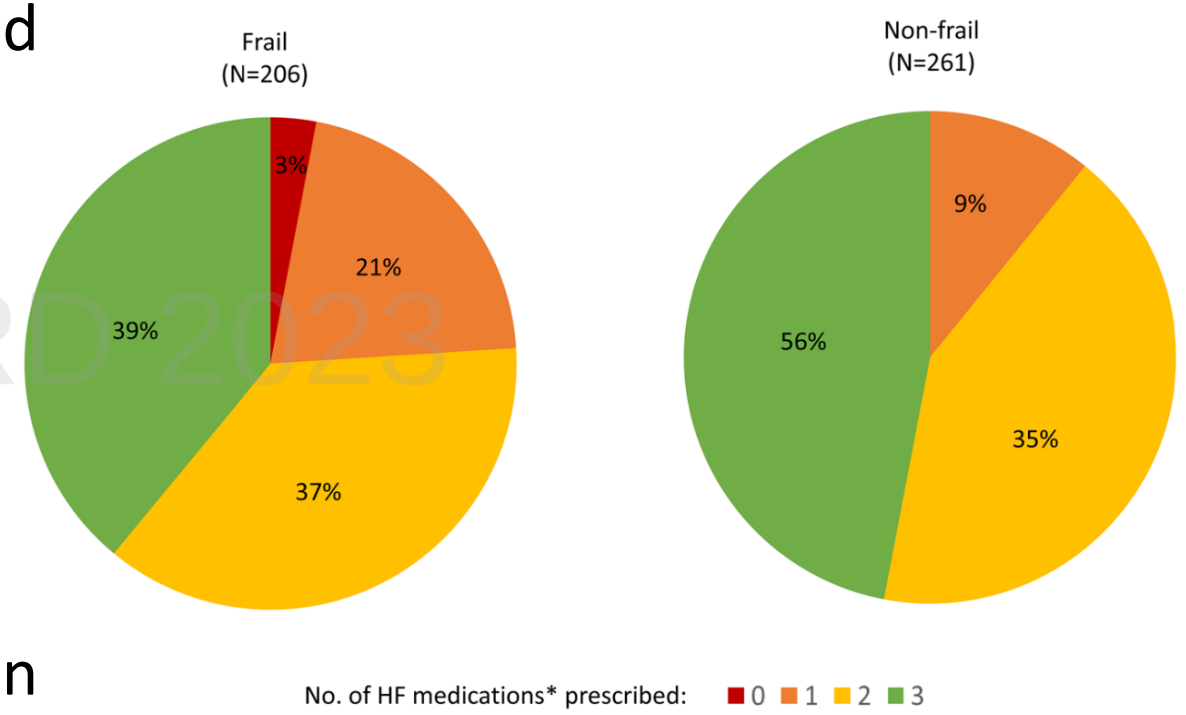
Values
AF =

Among HF subtypes, the prevalence of frailty is higher in patients with chronic stable HFpEF versus HFrEF, with up to 60% to 90% of patients with HFpEF identified as frail.

Sze S et al. Clinical Research in Cardiology. 2021

Common Problems with Medical Therapy of HF in The Elderly with Frailty

- Underuse and under-dosage of recommended pharmacotherapies with known mortality benefit
- Comorbidities are common, aggravate HF, complicate therapy and increase the total HF burden
- Response to diuretics, ACE inhibitors, b-blockers and/or positive inotropes may be diminished
- Frailty and cognitive impairment are common and lead to reduced compliance



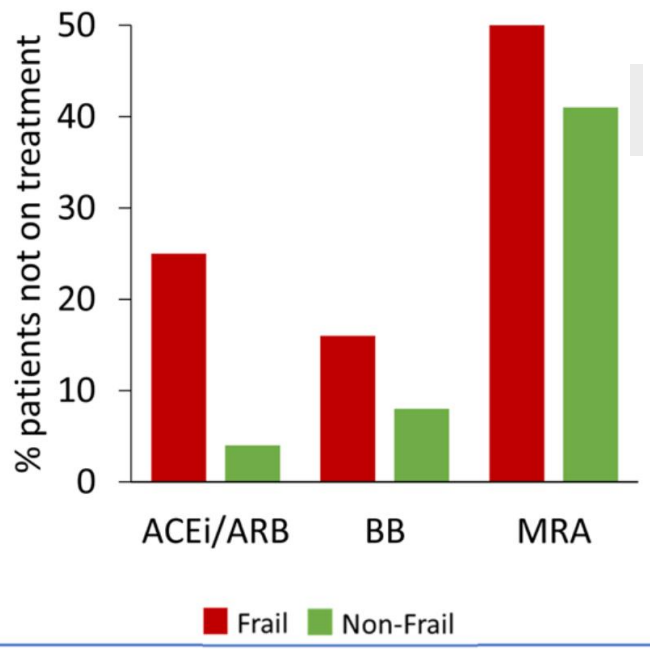
Number of HF medications prescribed for patients with HeFREF according to frailty status. *HF medications refer to ACEi/ ARB, beta-blockers and MRA

Butt JH et al. Journal of American College of Cardiology. 2022
Sze S et al. Clinical Research in Cardiology. 2021

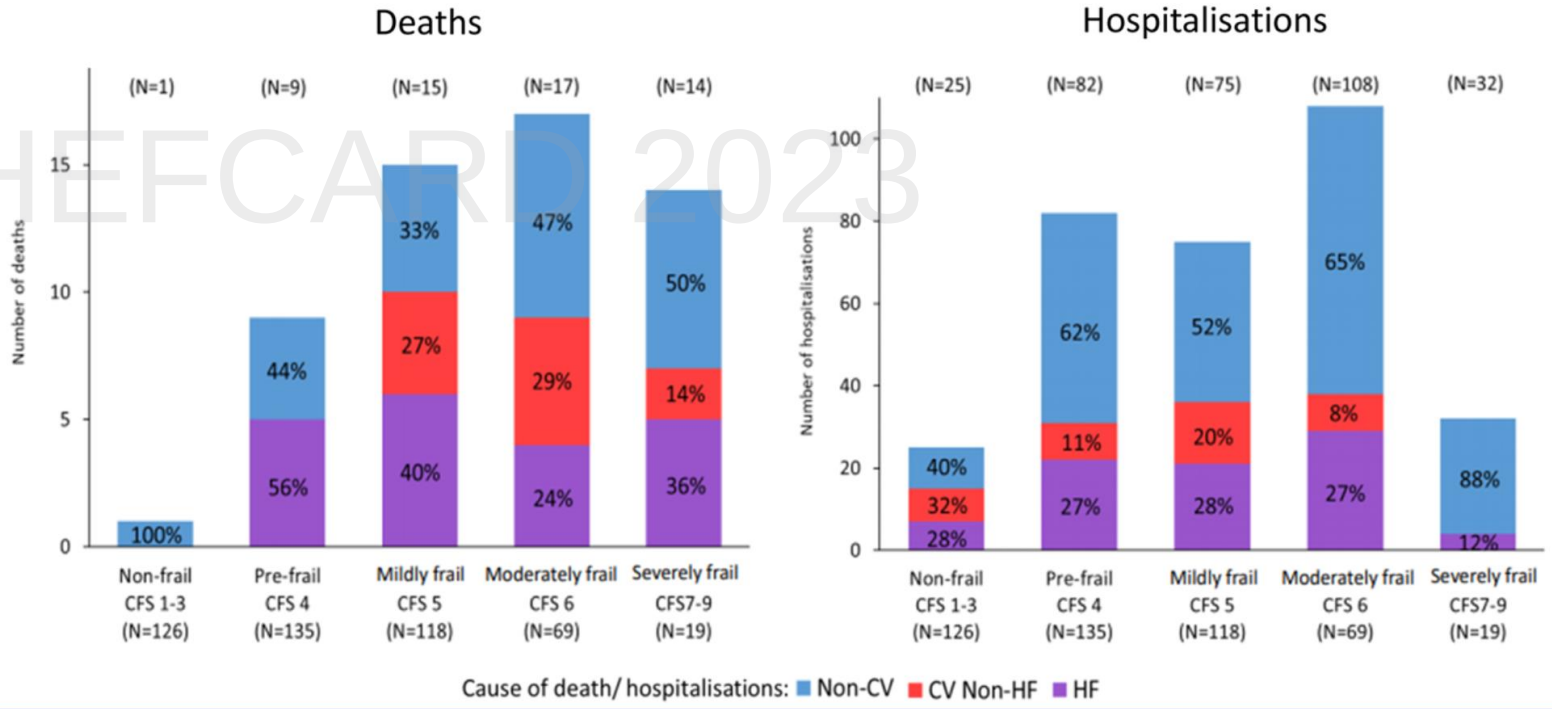
How does frailty affect treatment, hospitalisation and death in patients with chronic heart failure ?

467 patients with CHF [median age 76 years, median NT-proBNP 1156 ng/L, 44% frail (Clinical Frailty Scale >4)]

Suboptimal medical treatment in those with reduced ejection fraction



Higher deaths & hospitalisations at 1 year, most of which are non-cardiovascular



Sze S et al. Clinical Research in Cardiology. 2021

The Risk of Delaying or Omitting GDMT in HF Patient

HF with EF ≤40%

Lack of Initiation, Titration, or Persistence of:

Beta-Blocker

- ↑ *34%-35% relative risk of all-cause mortality*
- ↑ *19%-24% relative risk of all-cause mortality or hospitalization*

MRA

- ↑ *24%-35% relative risk of all-cause mortality*
- ↑ *35%-42% relative risk of HF hospitalization*

ARNI

- ↑ *~25% relative risk of all-cause mortality vs putative placebo*
- ↑ *~30% relative risk of CV mortality or HF hospitalization vs putative placebo*

SGLT2i

- ↑ *13% relative risk of all-cause mortality*
- ↑ *31% relative risk of HF hospitalization*

HF with EF >40%

Lack of Initiation or Persistence of:

SGLT2i

- ↑ *20% relative risk of CV mortality or HF hospitalization*
- ↑ *26% relative risk of HF hospitalization*

Delaying or Omitting GDMT in Eligible Patients With Heart Failure Associated With:

- Patient never being initiated on GDMT, or substantial delay
- Worse quality of life and health status
- Excess risk of disease progression
- Preventable deaths and hospitalizations

The risks of delaying or omitting guideline-directed medical therapy (GDMT) in eligible heart failure (HF) patients are substantial. ARNI = angiotensin receptor/neprilysin inhibitor; CV = cardiovascular; EF = ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Fonarow GC et al. JACC. 2023

Case Illustration

- 76-year-old male
- NYHA fc II, last rehosp 2 mo before coming to Oupatient clin
- Loss follow up and control since COVID era
- History of ACS 2020 and PCI 2 stents LAD (complete revasc)
- RF : ex smoker, HT
- Comorbidities : HT
- Current th/ :
  - Aspirin 80 mg
  - Atorvastatin 20 mg
  - Ramipril 5 mg
  - Digoxin 0.25 mg od
  - Bisoprolol 1. 25 mg (not routinely)
  - Spironolactone 25 mg
  - Furosemide 40 mg
  - ISDN 5 mg prn
- At OPC : BP 105/68 mmHg, HR 94 x/min, RR 22 x/min

  Status NYHA fc II

LAB Findings

- BW 65 kg
- Hb 12.4 g/dl
- Creatinin 1.3 mg/dl
- eGFR 57 ml/min/1.73m2
- HbA1c 6.2
- K 4.1 meq/L
- LDL 130 mg/dl

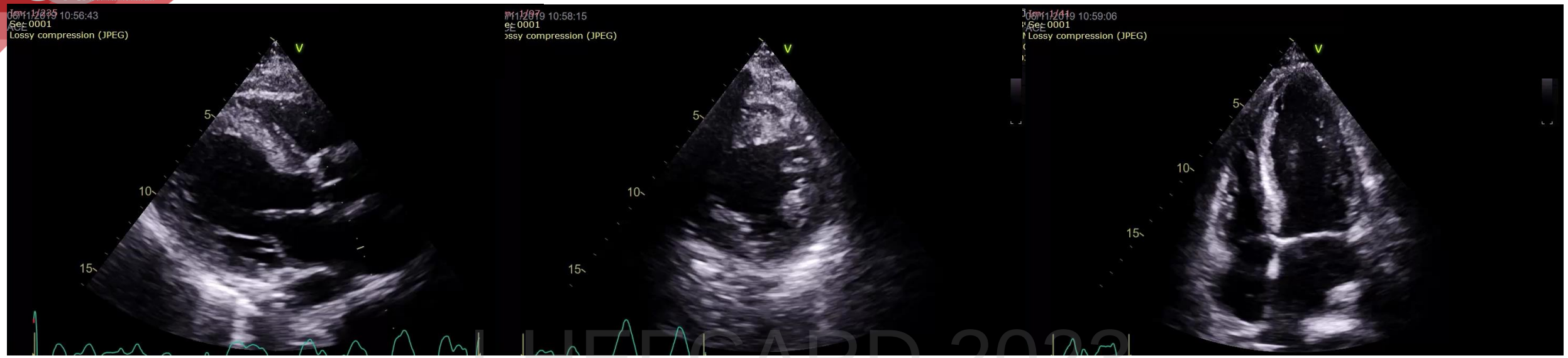
ECG

- Sinus rhythm , rate 94 x/min
- Q wave at anterior

Chest X Ray

- Cardiomegaly
- CTR 60%
- Cranialization (-)

Echocardiography



LV EF 32% (Simpson's Biplane)
Regional Wall Motion Abnormality (+)
Mild MR and TR
Normal RV systolic fc
Grade I diastolic dysfunction

Diagnosis :

- Stage C HFrEF / CHF ec CAD
- History of ACS
- NYHA fc II

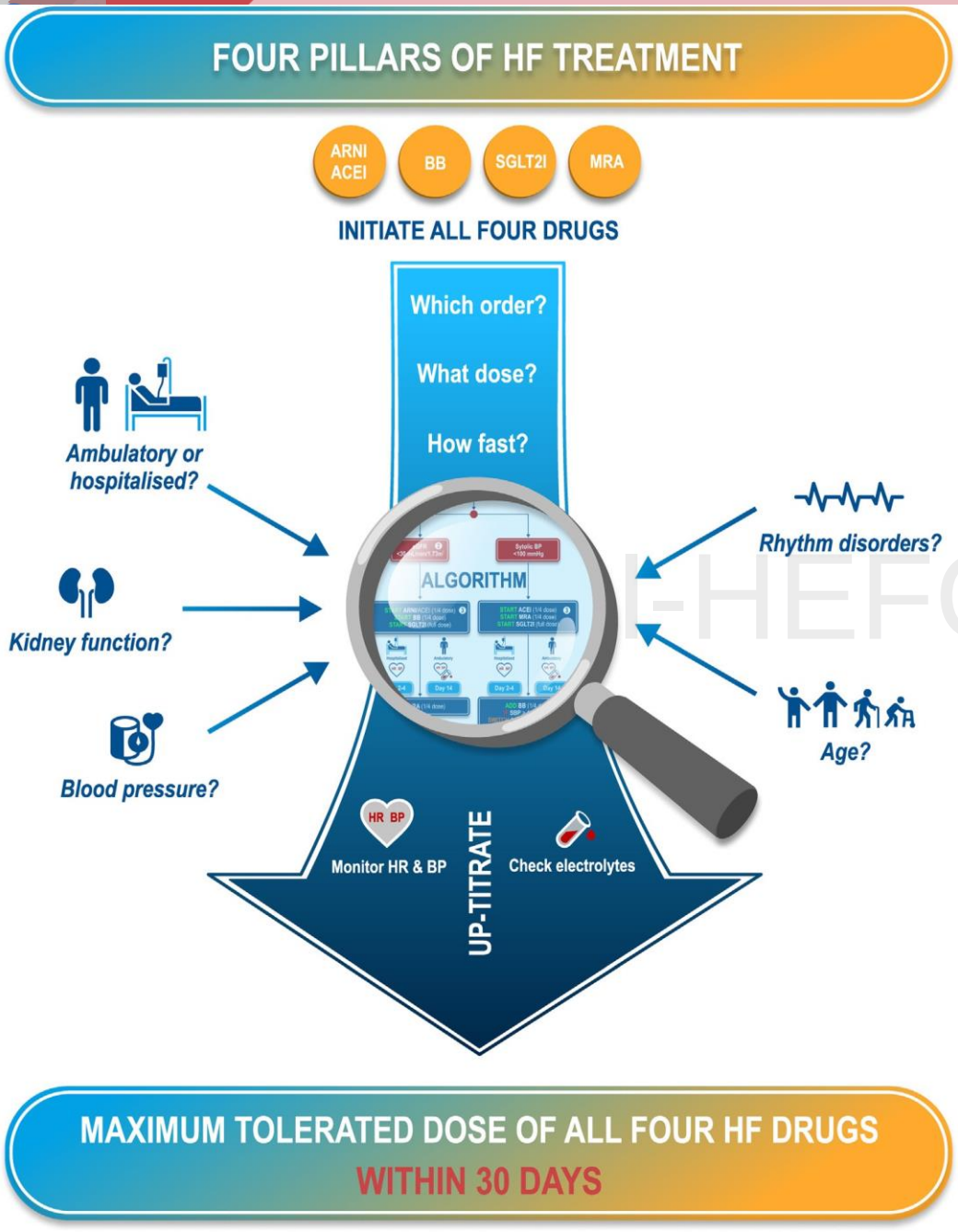
Issues :

- HFrEF despite complete revasc
- Prior rehosp
- Unoptimal GDMT
- Elderly

Question 1

What did the Guidelines say ?

Pharmacological treatments indicated in patients with HF



Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

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ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

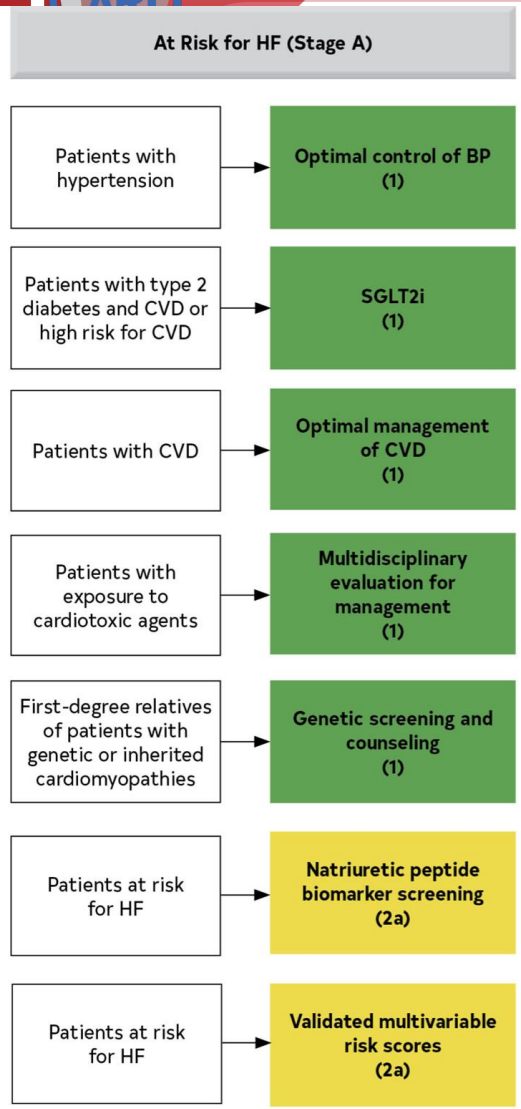
[a]Class of recommendation.

[b]Level of evidence.

Boureau AS et al. ESC heart Failure. 2022
McDonagh T, et al. European Heart Journal .2021

Question 2

What about HFmrEF?



Pharmacological treatments to be considered in patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction

ESC

Recommendations	Class	Level
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

www.escardio.org/guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Heidenreich, et al. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*
Vericiguat	2.5 mg *o.d.*	10 mg *o.d.*
Digoxin	62.5 µg *o.d.*	250 µg *o.d.*
Hydralazine/	37.5 mg *t.i.d.*/20 mg *t.i.d.*	75 mg *t.i.d.*/40 mg *t.i.d.*

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; *b.i.d.* = bis in die (twice daily); CR = controlled release; CV = cardiovascular; MRA = mineralocorticoid receptor antagonist; *o.d.* = omne in die (once daily); SGLT2 = sodium-glucose co-transporter 2; *t.i.d.* = ter in die (three times a day); XL = extended release.

[a]Indicates an ACE-I where the dosing target is derived from post-myocardial infarction trials.

[b]Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive randomized, placebo-controlled trial and the optimum dose is uncertain.

[c]Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg *b.i.d.* for those with a history of symptomatic hypotension.

[d]Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).

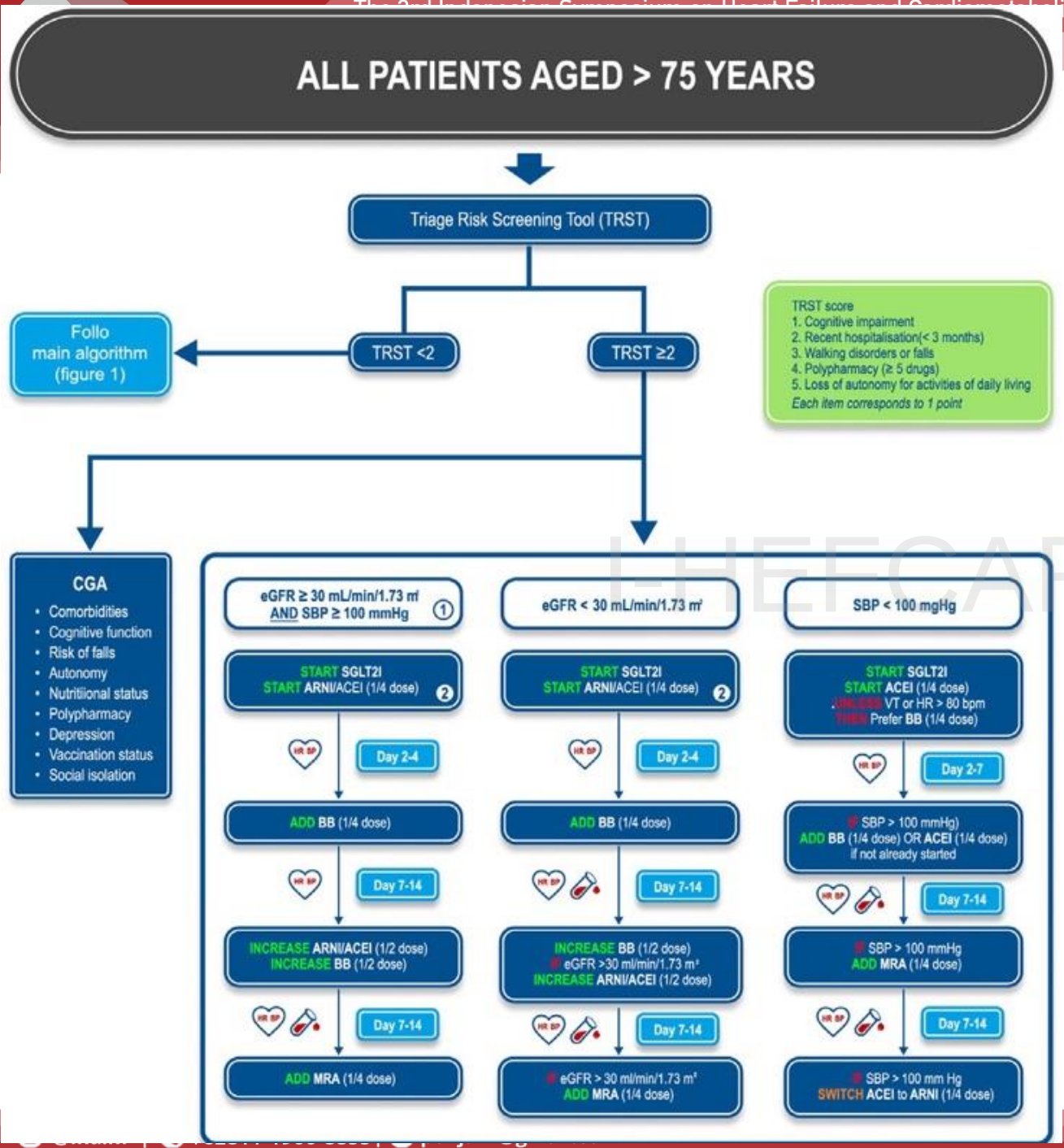
[e]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.

[f]Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

McDonagh T, et al. European Heart Journal.2021.

Question 3

When and how should we start GDMT in frailty patients?



- ✓ LIFESTYLE MODIFICATION
- ✓ TREAT OTHER COMORBIDITIES
- ✓ ACHIEVE TARGETS

STOP TITRATION in case of:
- SBP < 100 mm Hg
- Falls
- Orthostatic hypotension
- Decline in renal function

Objective at discharge or 30 days after treatment start

SGLT2I: full dose
ARNI and BB: ½ dose (or full dose if tolerated)
MRA: ¼ dose (or ½ dose if tolerated)

TITRATION OF THE FOUR MEDICATIONS ③

- UP-TITRATE EVERY 2 weeks until maximum tolerated dose is reached.
- INCREASE 1 - 2 MEDICATIONS AT THE SAME TIME.
- REDUCE DIURETICS whenever possible.
- CHECK RENAL FONCTION and SERUM POTASSIUM between each titration visit.
- CONSIDER TELEMONITORING for treatment optimisation.

Perform blood monitoring within 7 days of EACH drug introduction or escalation step.

Monitor heart rate and blood pressure following EACH medication change.

Boureau AS et al. ESC heart Failure. 2022

Table 3 Primary prevention of frailty and optimization care of geriatric syndromes in elderly HF subjects angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs) and angiotensin receptor neprilysin inhibitors (ARNIs) together with mineralocorticoid receptor antagonists (MRAs), sodium-glucose co-transporter 2 inhibitors (SGLT2i), beta-blockers (BB)

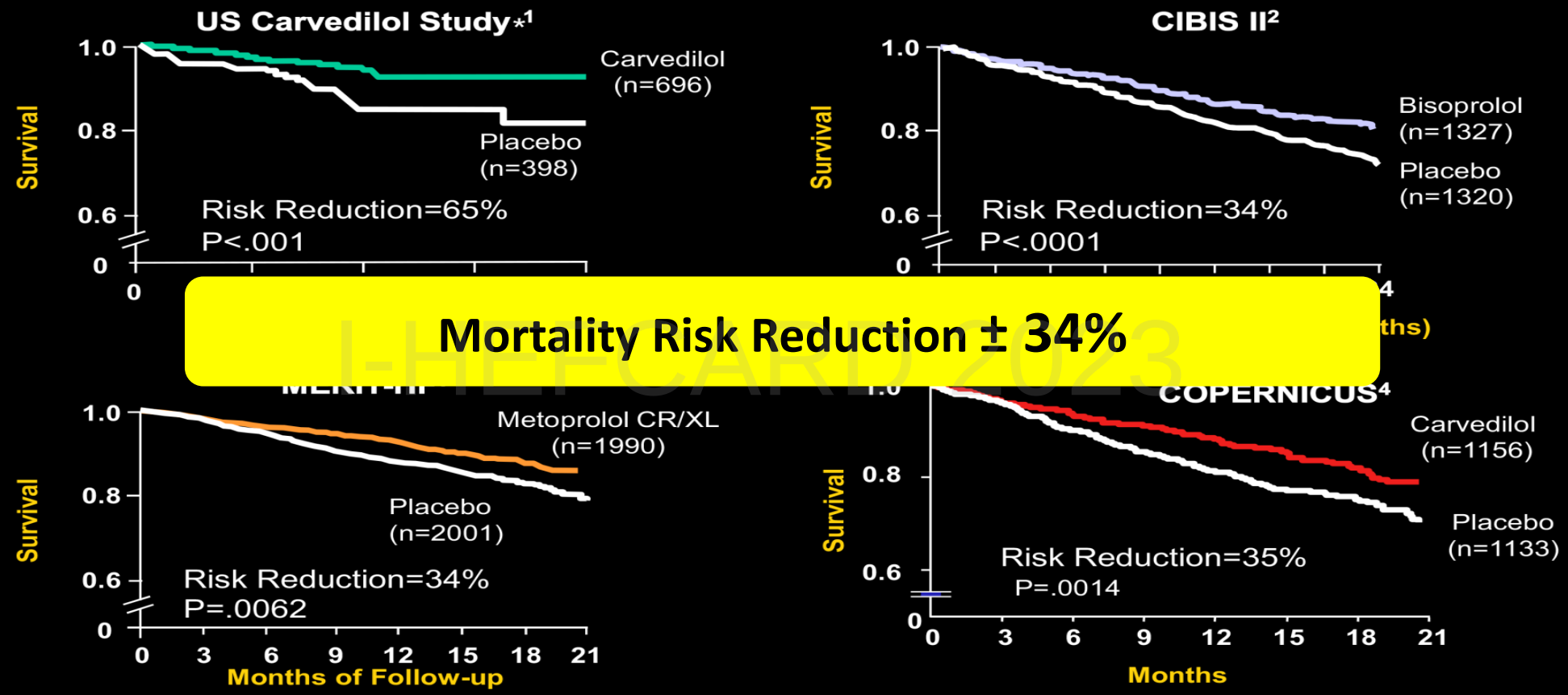
	Prevention	Treatment
HFrEF HFpEF	• Treatment of risk factors as cardiovascular chronic diseases: hypertension, diabetes, atrial fibrillation	• Optimal therapy (ACEi or ARNI, BB, MRA, SGLT2i)[29] • Refer to resynchronization if indicated • Optimal diuretic management adapted to co-morbidities therapeutics • Exercise training programme, 2–3 times/week
Co-morbidities and polypharmacy	• Treatment doses management according to renal clearance • Try to use a single drug to treat two or more diseases[30] • Patient and caregiver information about each medication	• Check co-morbidities management including iron deficiency • Priority setting for patients with multiple co-morbidities • Medication review
Sarcopenia	• Regular physical exercise adapted to patient capacity	• Exercise training programme, which includes aerobic, strength, and balance exercises, 2–3 times/week • Combination of nutrition and exercise programmes
Malnutrition	• Weight monitoring • Protein intake: 1 to 1.2 g/kg/day • Regular physical exercise adapted to patient capacity	• Energy input of 30 to 40 kcal/kg/day • Protein intake: 1.2 to 1.5 g/kg/day • +/− oral nutritional supplements • Regular physical exercise adapted to patient capacity
Physical function and falls	• Screen for orthostatic hypotension • Sufficient water supply • Regular physical exercise adapted to patient capacity	• Identify and treat risk factors including psychotropic drugs reduction • Search for potential precipitating risk factors • Vitamin D supplementation[31] • Environmental assessment • Exercise training programme, which includes aerobic, strength, balance and flexibility exercises, 2–3 times/week
Depression	• Combatting Social Isolation	• Medication if needed: selective serotonin reuptake inhibitors • Psychotherapy
Cognitive impairment	• Treatment of chronic diseases such as hypertension or atrial fibrillation to prevent cognitive decline. • Social participation	• Specific attention to drug adherence (home help to deliver treatments) • Specific treatments and social support • Cognitive stimulation
Vaccination	• Influenza, pneumococcal, SARS-CoV2	
Social	• Therapeutic compliance screening	• Social support • Nurses for treatment

Boureau et al. ESC Heart failure. 2022

Question 4

Why should we use BB?

β -blocker Evidence: Benefit in HF and LVSD



[1]Packer M et al. N Engl J Med.1996;334:1349-1355. [2]CIBIS II Investigators and Committees. Lancet. 1999;353:9-13.
[3]MERIT-HF Study Group. Lancet.1999;353:2001-2007.

Age of Patients in Major Trials of β-Blocker in HF

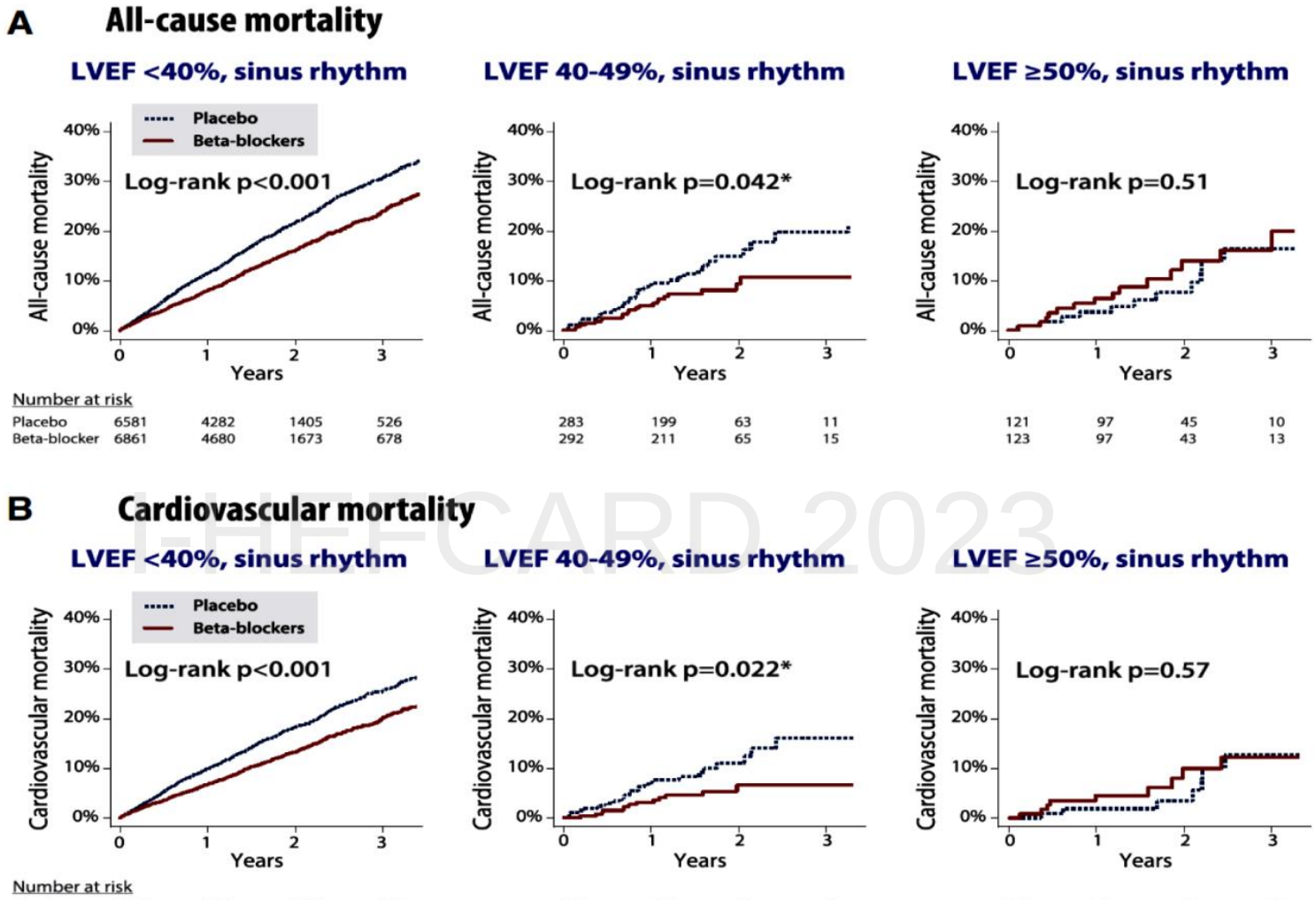
Trial	β-Blocker	N	Mean Age	% Females	EF(%)
COPERNICUS	Carvedilol*	2289	63	21	19.9
MERIT-HF	Metoprolol*	3991	64	23	28.0
US Carvedilol	Carvedilol*	1094	58	22	22.6
CIBIS-II	Bisoprolol	2647	61	20	27.5
Mean			*61*	*21.5%*	*24.9*
US Heart Failure Population			**77**	**50**	**>50%****

* Agents approved for the treatment of HF in the US

** Percentage of US population with preserved ejection fraction

MERIT-HF Study Group. *Lancet.* 1999;353:2001-2007; Packer *N Engl J Med.* 2001;344:1651-1658; Colucci WS. *Circulation.* 1996;94:2800-2806; CIBIS Investigations and Committees. *Lancet* 1999;353:9-13; The Beta-Blocker Evaluation of Survival Trial Investigators. *N Engl J Med.* 2001;344:1659-1667; Heiat et al. *Arch Intern Med.* 2002;162:1682-1688.

In Previous BB trials, populations were younger with Lower EF, meanwhile HF prevalence mostly in older patient with good LVEF



Previous Beta blocker only decerased all cause mortality and Cardiovascular mortality in HF reduced and midrange EF

SENIORS

Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

A randomised, double-blind, placebo-controlled phase III study

Table 2. Summary of randomized control clinical trials in heart failure with reduced ejection fraction. LVEF: left ventricular ejection fraction, NYHA: New York Health Association.

Trial	Year	Type of β-Blockers	n° of Patients	Inclusion Criteria	Effects on Mortality
CIBIS	1994	Bisoprolol	641	LVEF < 40%, NYHA class III-V	No significant difference in mortality between the two groups
MERIT HF	1999	Metoprolol	3991	LVEF < 40%, NYHA class II-IV	34% relative risk reduction in all-cause mortality
CIBIS II	1999	Bisoprolol	2647	LVEF < 35%, NYHA class III-IV	34% relative risk reduction in all-cause mortality
CAPRICORN	2001	Carvedilol	1959	Previous AMI and LVEF < 40%	23% relative risk reduction in all-cause mortality
COPERNICUS	2001	Carvedilol	2289	LVEF < 25% and NYHA class III-IV	31% relative risk reduction in all-cause mortality
COMET	2003	Metoprolol vs Carvedilolo	2309	LVEF < 35% and NYHA class II-IV	17% relative risk reduction in all-cause mortality in carvedilol group
SENIORS	2005	Nebivolol	2128	LVEF < 35%, NYHA class II-IV, age > 7o years	No significant difference in mortality between the two groups

The Rationale for the SENIORS Trial

SENIORS explored **different population** from previous BB studies:

New subset population → based on Euro and US HF Population Studies **(women, older ,despite EF)**

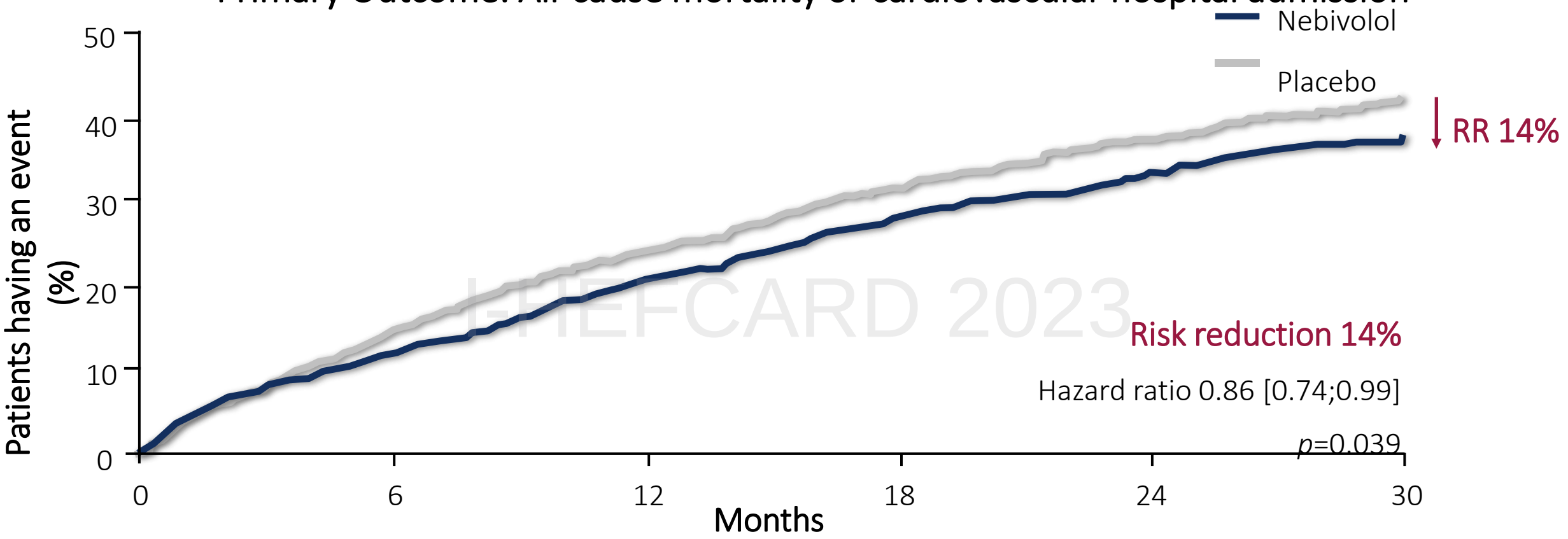
Nebivolol, unlike other selective β_1-antagonists:

- maintains stroke volume[1]
- maintains cardiac output (despite the bradycardi effect)[1]
- reduces systemic vascular resistances[2]
- increases the ejection fraction[3]
- improves early diastolic relaxation[2]
- causes less pronounced heart rate and cardiac contractility reductions[4]

[1]Münzel T, Gori T. J Am Coll Cardiol. 2009;54:1491-9.
[2]Nodari S, at al. Eur J Heart Failure 2003;5:621-7.
[3]Brehm BR, et al. Eur J Heart Fail. 2002;4:757-63.
[4]Agabiti Rosei E, Rizzoni D. Drugs. 2007;67:1097-107

Seniors Trial

Primary Outcome: All-cause mortality or cardiovascular hospital admission

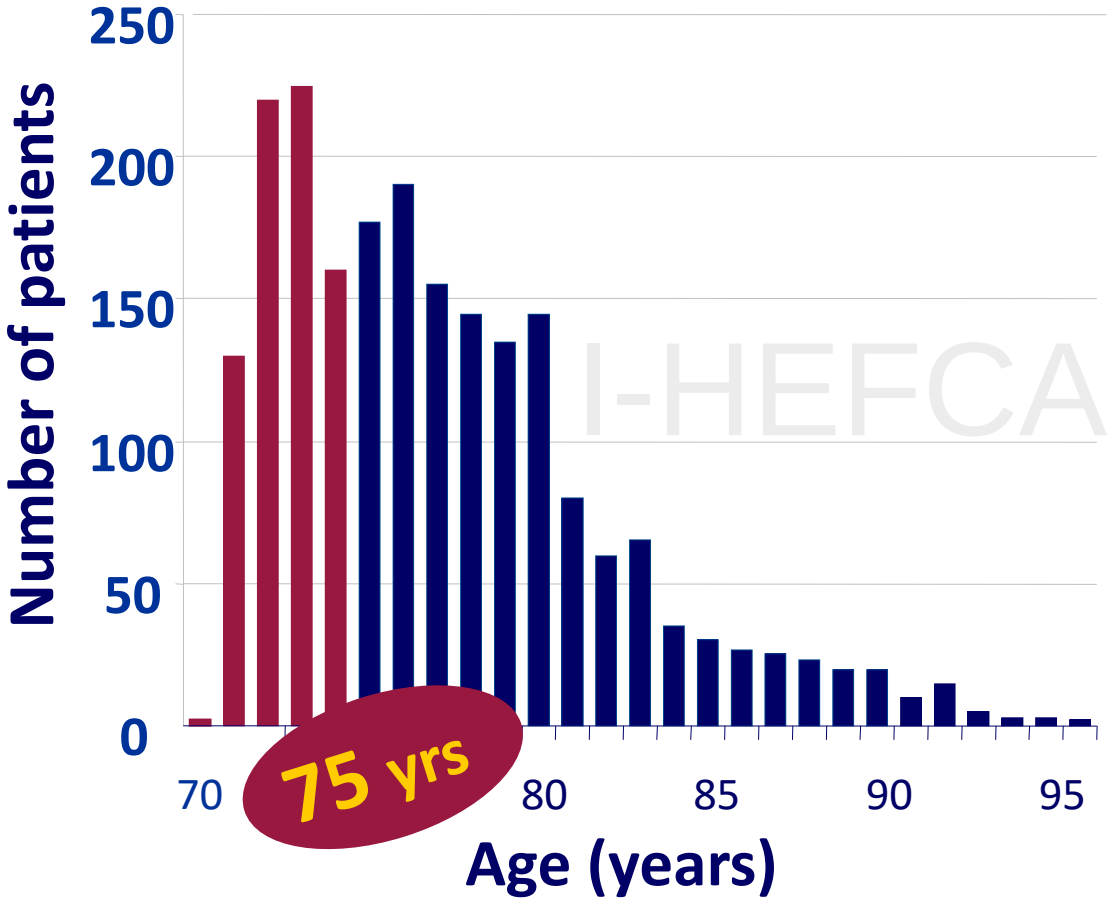


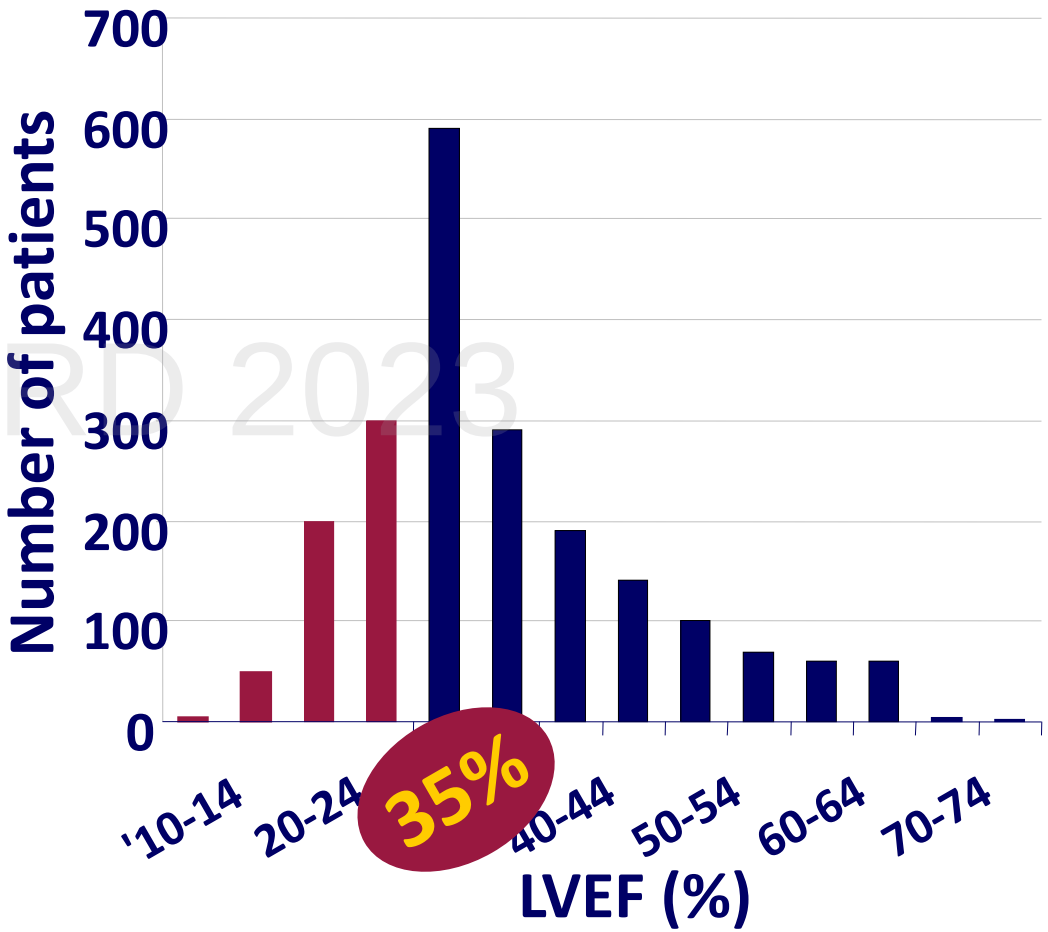
N. of events:
nebivolol 332 (31.1%); placebo 375 (35.3%)

Study aim: to assess effects of nebivolol in patients 70 years with a history of heart failure (n=2128), regardless of ejection fraction. Parallel group, randomised, double-blind, multicentre, international trial. Patients were randomly assigned to nebivolol (titrated from 1.25 mg once daily to 10 mg once daily, n=1067) or placebo (n=1061). Mean duration of follow-up was 21 months.

Flather MD, *et al. Eur Heart J* 2005;26:215-25.

SENIORS subgroups which most closely resemble previous studies





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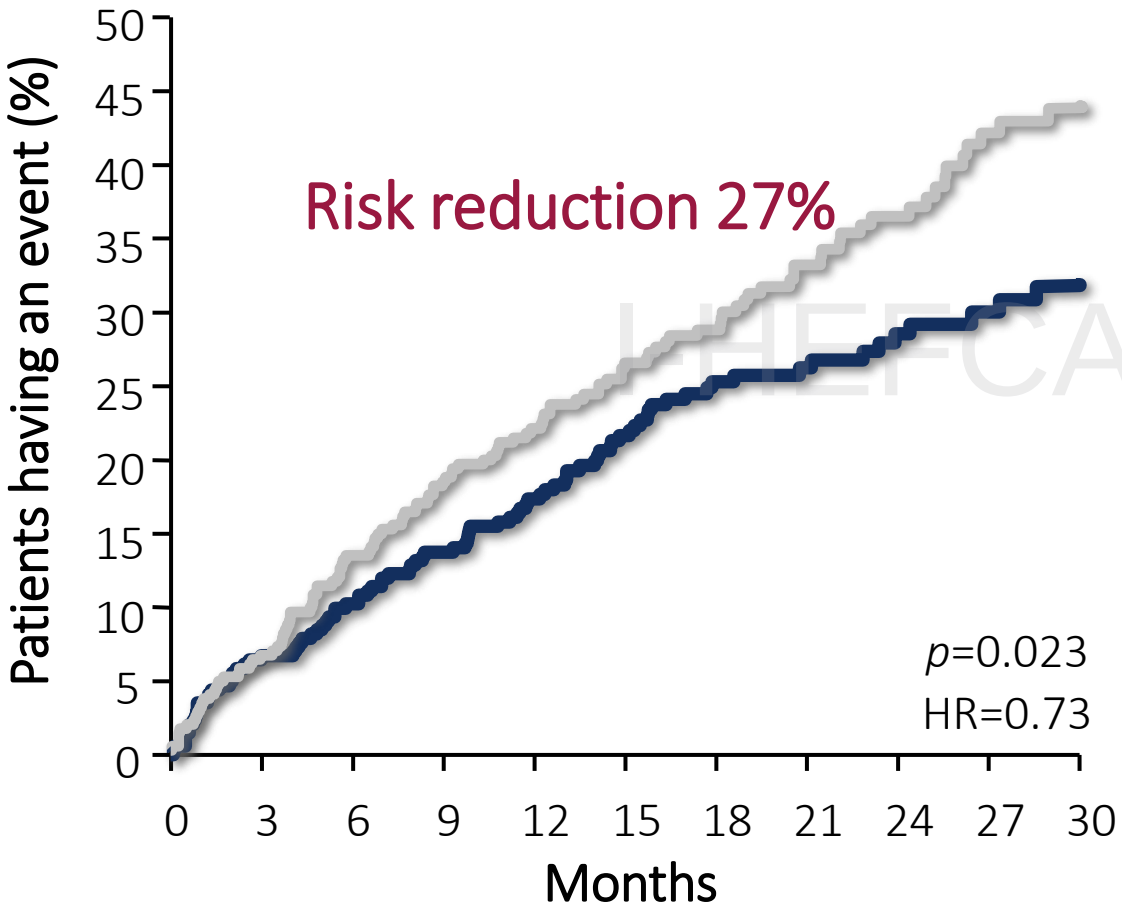
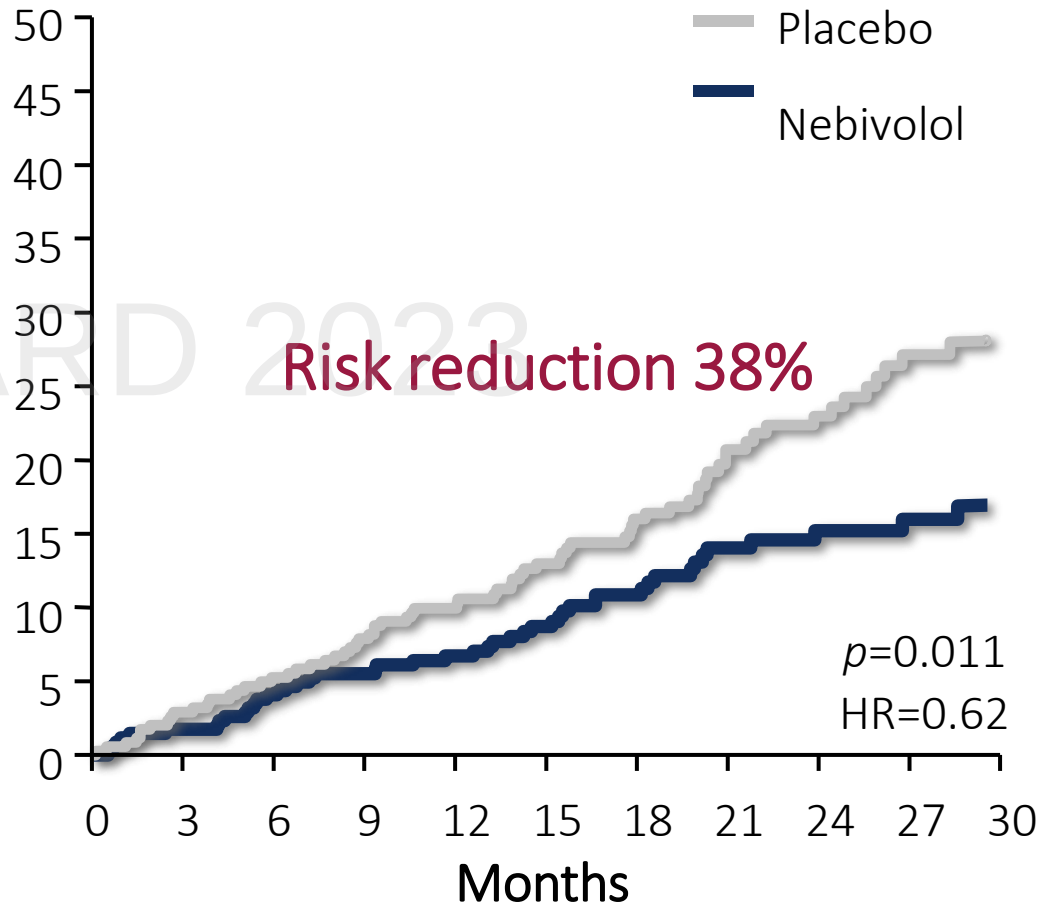
Flather MD, *et al. Eur Heart J* 2005;26:215-25.

The SENIORS trial - subgroup analysis: age < 75.2 years and LVEF ≤ 35%

All-cause mortality or CV hospitalisation



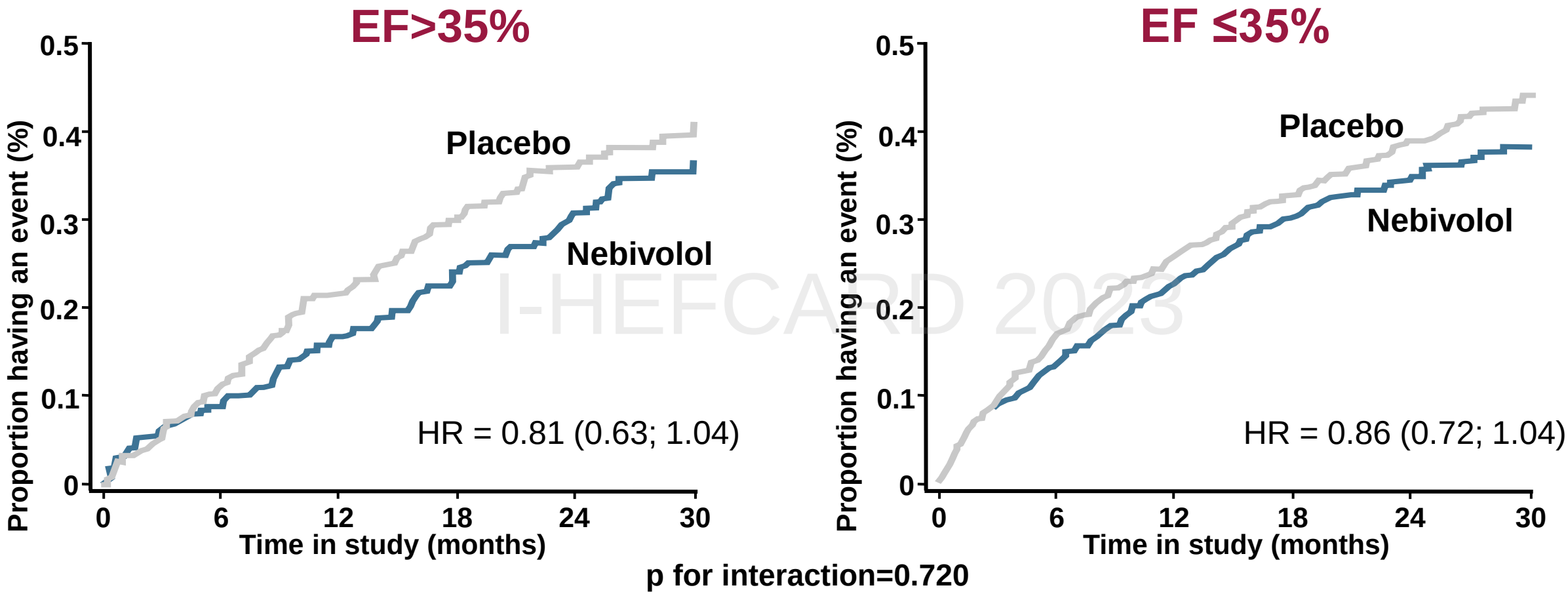
All-cause mortality



Adapted from Flather MD, *et al. Eur Heart J* 2005;26:215-25.

Study aim: to put the results of SENIORS (a parallel group, randomised, double-blind, multicentre, international trial. Patients were randomly assigned to nebivolol [titrated from 1.25 mg once daily to 10 mg once daily, n=1067] or placebo (n=1061). Mean follow-up: 21 months) in the context of previous beta-blocker trials, data were extracted for 684 HF patients treated with nebivolol 1.25 mg to 10 mg od (n=342) or placebo (n=342).

SENIORS – All-cause mortality or CV hospitalisation according to EF



There was no difference in the effect of nebivolol versus placebo between HF patients with impaired ejection fraction (EF) and patients with preserved EF. Although the SENIORS trial was not powered to show a statistically significant effect of nebivolol in the EF subgroups, the Hazard Ratios are similar with no apparent evidence of interaction in any subgroup analysis, which supports the hypothesis that there is a similar beneficial effect in patients with impaired and preserved EF.

Adapted from Flather MD, *et al. Eur Heart J* 2005;26:215-25.

Adapted from van Veldhuisen DJ, et al. J Am Coll Cardiol. 2009;53:2150-8.

Initial condition :
BP 105/68 mmHg, HR 94 x/min
A1c 6.2 / Cr 1.3 / eGFR 57 /**recent rehosp/**
Underuse and under-dosage GDMT
Th/

- Aspirin 80 mg
- Atorvastatin 20 mg
- Ramipril 5 mg
- Digoxin 0.25 mg od
- Bisoprolol 1.25 mg (not routinely)
- Spironolactone 25 mg
- Furosemide 40 mg
- ISDN 5 mg prn

2 mos post initiation :
BP 98/75 mmHg
HR 78 x/min
WBC 6100/mm3
Cr 1.4 mg/dl
eGFR 52 ml/min/1.73m2
Glycosuria (-)
Uptitrate nebivolol to 2,5 mg
Not using digoxin

Monitoring :
BP 95-110/60-72 mmHg
HR 60-68x/min
Cr 1.2 – 1.5 mg/dl
eGFR 48-62 ml/min/1.73m2
A1C 5.4 – 5.8
No signs of Hypoglycemia / Hypovolemia
EF 32-36% (simpson's Biplane)
No history of hosp

2020 → 2022 → 2023

CASE STUDY

1 mo post routinely nebivolol 1,25 mg :
BP 98/75 mmHg
HR 82 x/min
WBC 6500/mm3
Cr 1.6 mg/dl
eGFR 45 ml/min/1.73m2
Adding SGLT2i

Current Medication :

- Aspirin 80 mg
- Atorvastatin 20 mg
- Ramipril 10 mg
- Nebivolol 5 mg
- Spironolactone 25 mg
- Dapagliflozin 10 mg

No Diuretic
No History of hosp

Beta Blocker SUMMARY

WHY **BB** is indicated to improve QoL, reduce the risk of HF rehospitalization, and reduce mortality

WHEN BB should be initiated as quickly and safe as possible

WHO BB should be initiated in all symptomatic HFrEF patients (include elderly patients)

HOW BB starts low, goes slow

WHERE In safety considerations, pasien should have stable hemodynamic and clinical status. Patient not in inotropic drug (inhospitalised) or outpatients setting

WHAT TO MONITOR For long term monitoring, assess renal function, body weight, and heart rate, blood pressure

Take Home Messages

- Frailty is common in older patients with heart failure, and both frailty and heart failure share common mechanistic features, including strong relations with a high burden of comorbidities, inflammation, and sarcopenia.
- Frailty is associated with worse clinical, functional, and quality of life outcomes in older patients with heart failure.
- Frailty should be considered for routine assessment by using well-validated assessment tools to better inform prognosis.
- Do not delay or omitting GDMT in HF patients with frailty

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