Recent Data and Evolving Management Aspects in Heart Failure

Hong Kong College of Cardiology ASC 2023

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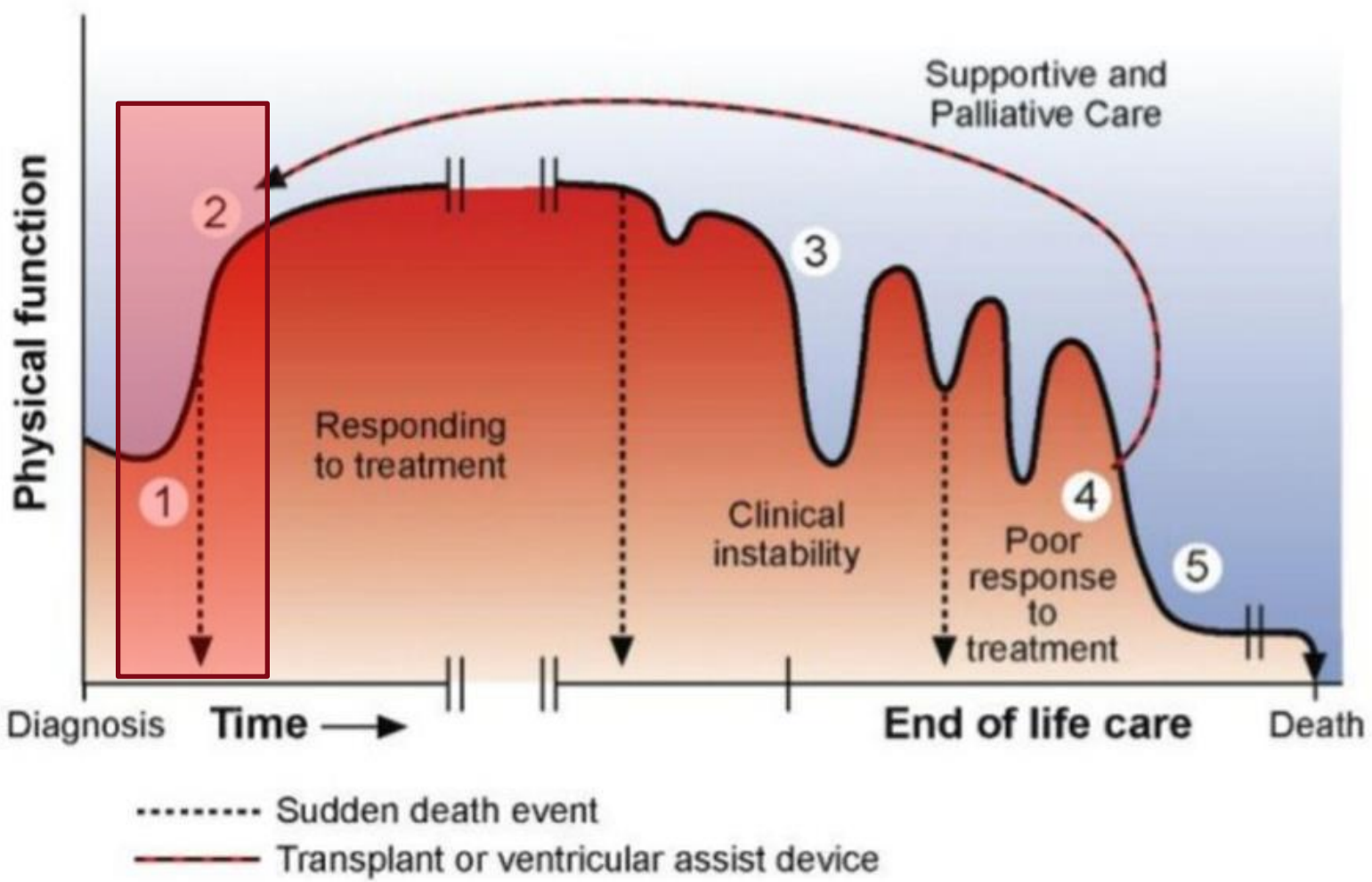
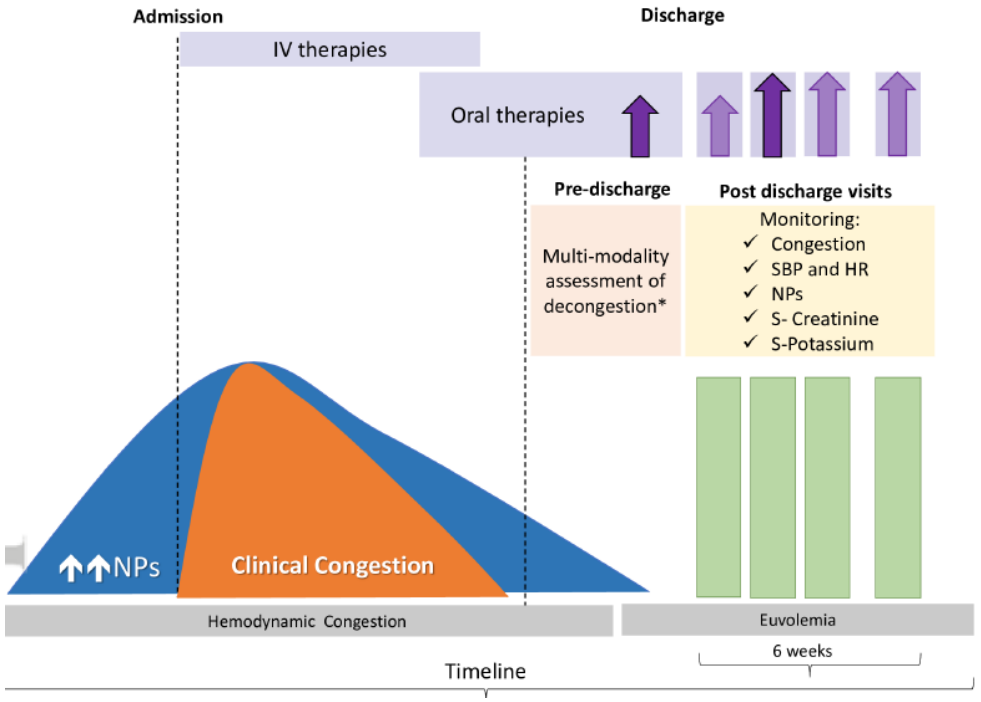
Heart Failure Trajectory



Pre and post discharge management



Optimal management in the early post-discharge phase is critical

1- it may prevent rehospitalizations through the detection and effective treatment of residual congestion.

2- initiate at pre discharge and **titration** to target doses in the early post discharge period, of GDMT, may improve both short- and long-term outcomes.

3-Medical treatment is often left unchanged, so the **AHF hospitalization presents an opportunity for implementation of therapy.**

Pre and post discharge management

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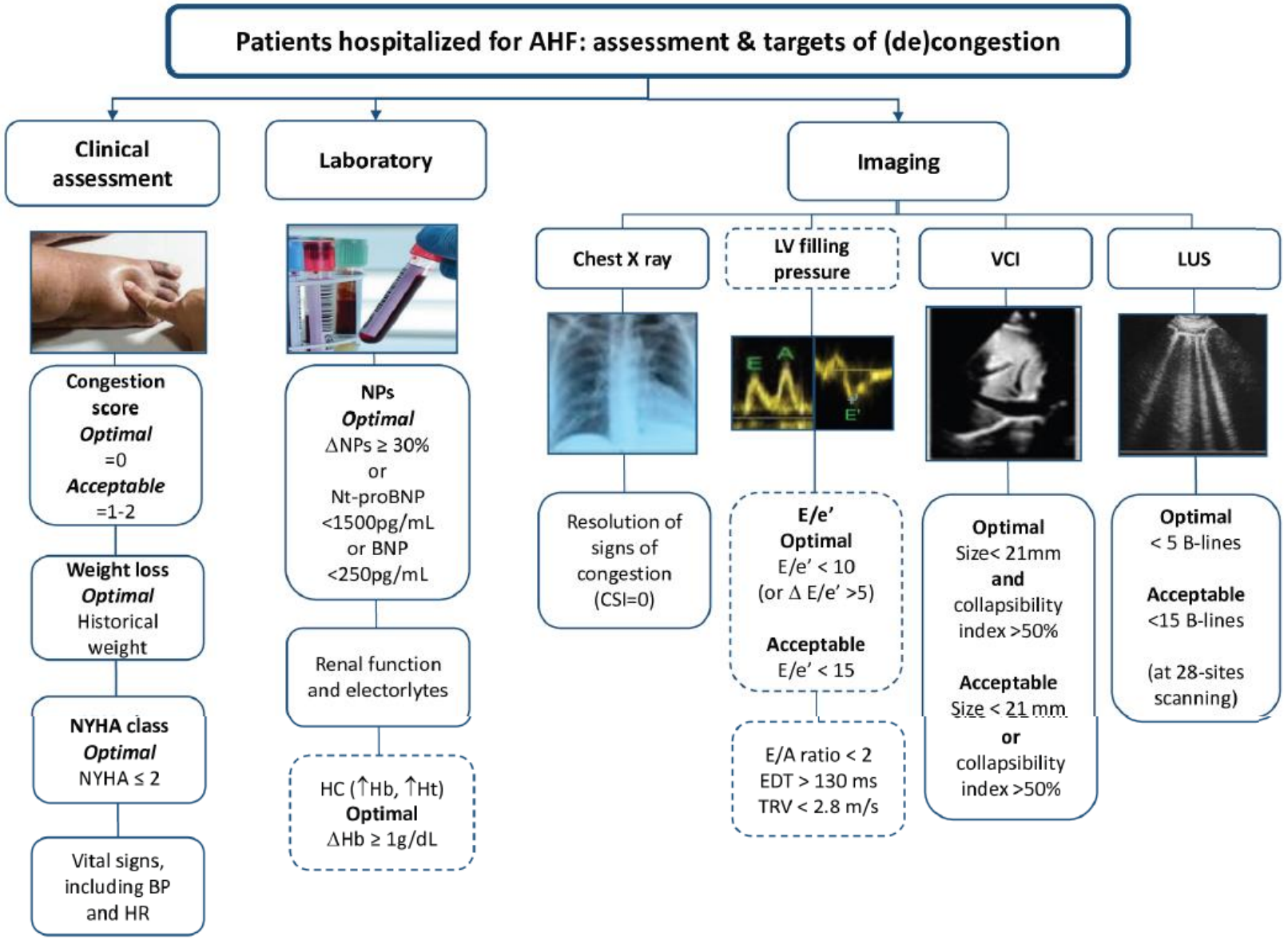

Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: a scientific statement by the Heart Failure Association (HFA) of the ESC

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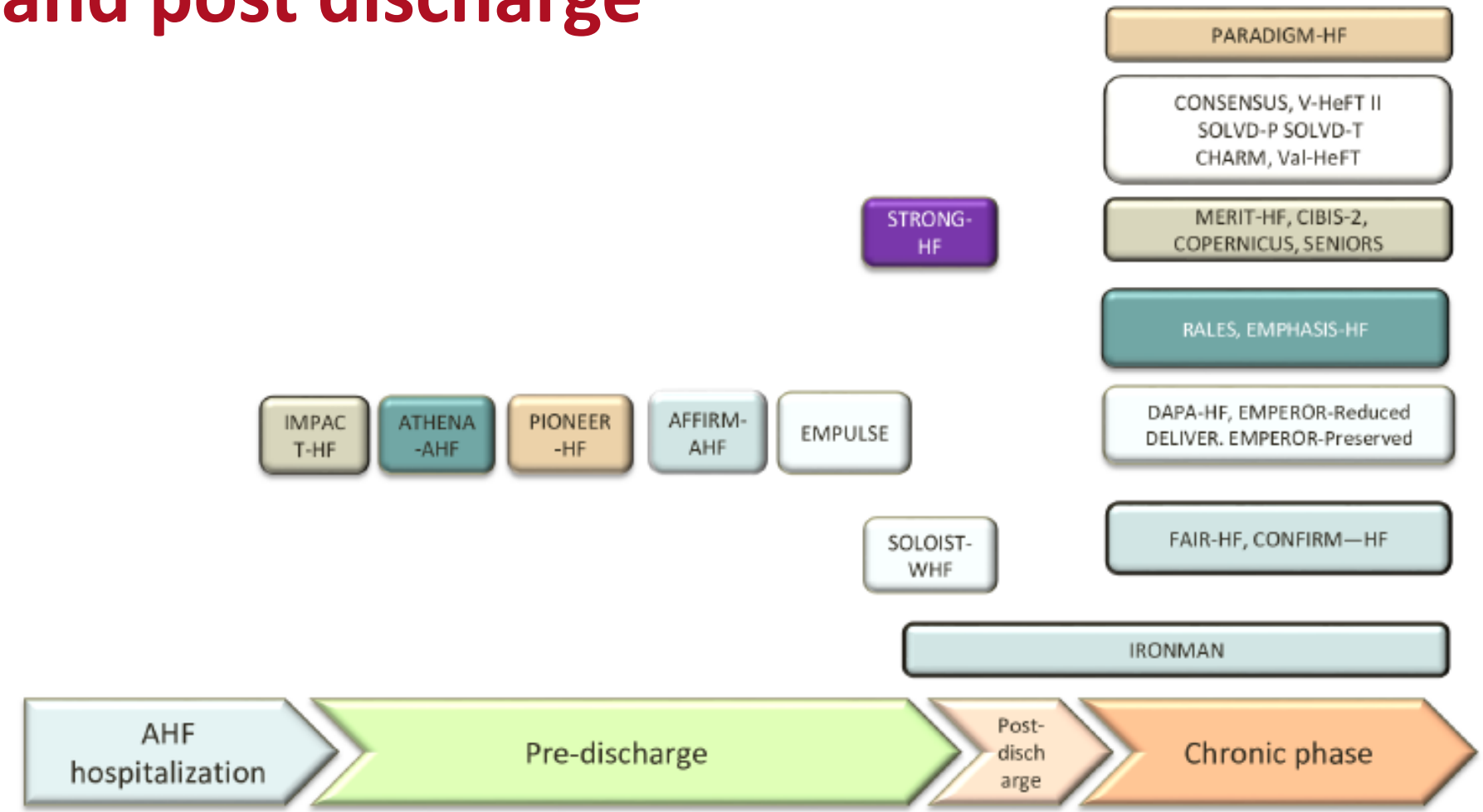
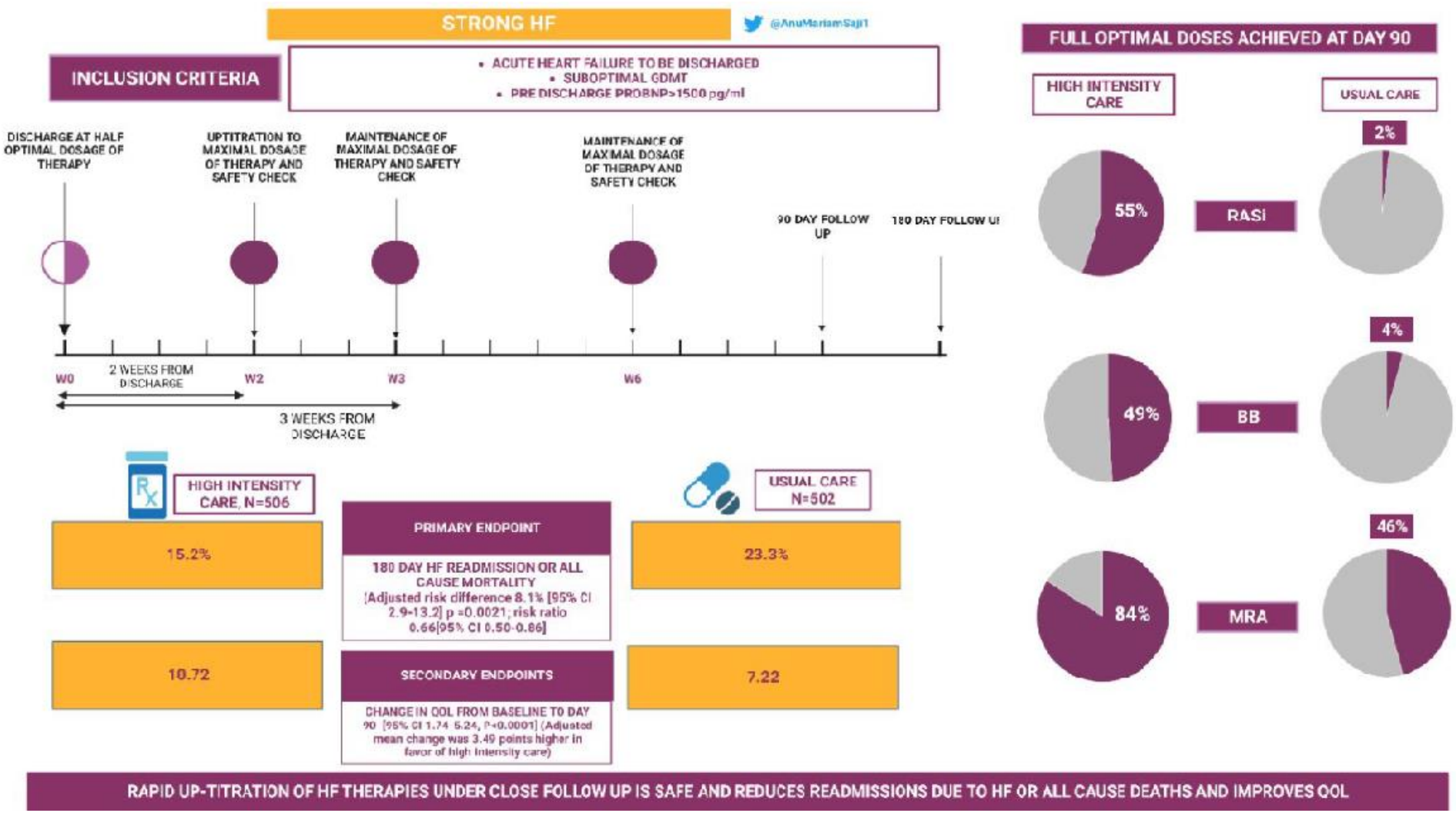
Pre and post discharge

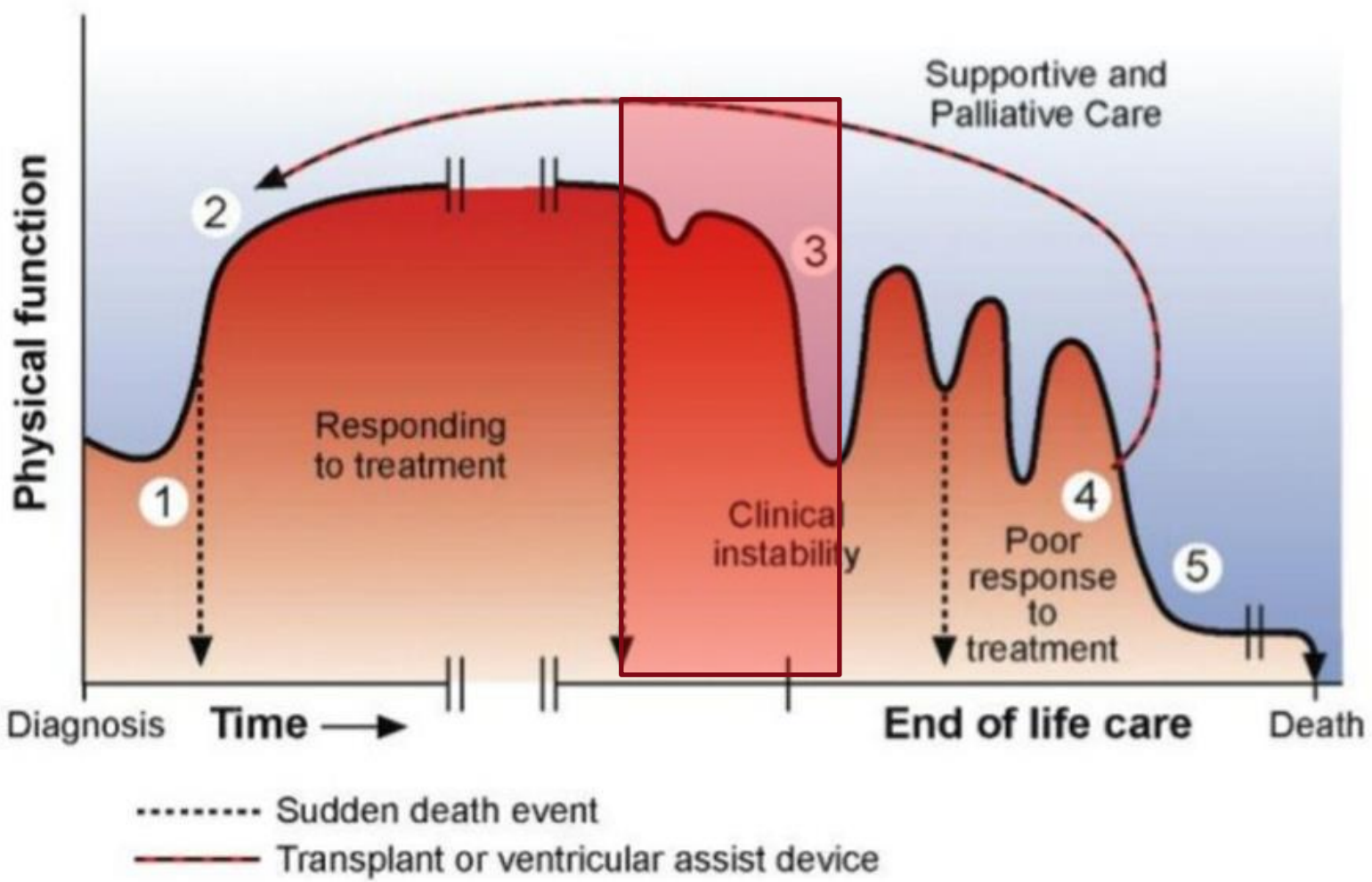


Strong HF trial



Mebazaa A et al. Lancet 2022;400:1938-52

Heart Failure Trajectory



Worsening HF

	Includes	Excludes
Definition	• Worsening symptoms and signs of HF • Requiring intensification of treatment, generally including diuretic therapy • Occurring in patients with pre-existing HF	• New-onset HF • Episodes with concomitant factors, including comorbidities and/or poor compliance, as primary cause
Pathophysiology	• Disease progression • Congestion	• Precipitating factors as main cause
Site of care	• Hospital • Emergency department • Ambulatory – with IV therapy – with escalation of oral therapy	• Episodes requiring no changes in HF treatment

≠ acute HF which is a much broader entity including also new onset HF as well as different clinical presentations such as acute pulmonary oedema, right ventricular failure and cardiogenic shock.

Worsening HF: a clinical consensus statement by the HFA of the ESC. European Journal of Heart Failure (2023) doi:10.1002/ejhf.2874

Worsening HF

HFA Heart Failure Association

Recurrent WHF episodes can be the preamble to lack of response to GRMT and trigger candidacy to HT, durable mechanical circulatory support and palliative care- **ADVANCED HF**

TREATMENT

In-hospital
Emergency Department
Outpatient

Treatment of congestion
Intensification of diuretic therapy
- Switch to intravenous loop diuretic
- Escalate oral dose of loop diuretic
- Switch to subcutaneous loop diuretic ?
- Add acetazolamide
- Add thiazide-like diuretics ?
- Other options (i.e. ultrafiltration)

Treatment of hypoperfusion
Intravenous inotropic therapy
- single administration/ Intermittent

Oral agents
- Digitalis glycosides
- New agents? [a]

PREVENTION

Start early, possibly before discharge[b]
Combine drugs as their effects are additive
Administer simultaneously or in rapid sequence

Neurohormonal antagonists and modulators
In patients with HFrEF
- ARNI /ACEI[b]
- Beta-blockers
- MRA

SGLT2i
In all patients
- Dapagliflozin or Empagliflozin

Intravenous iron supplementation
In patients with ID and LVEF <50%

sGC activators
In patients with LVEF <45%

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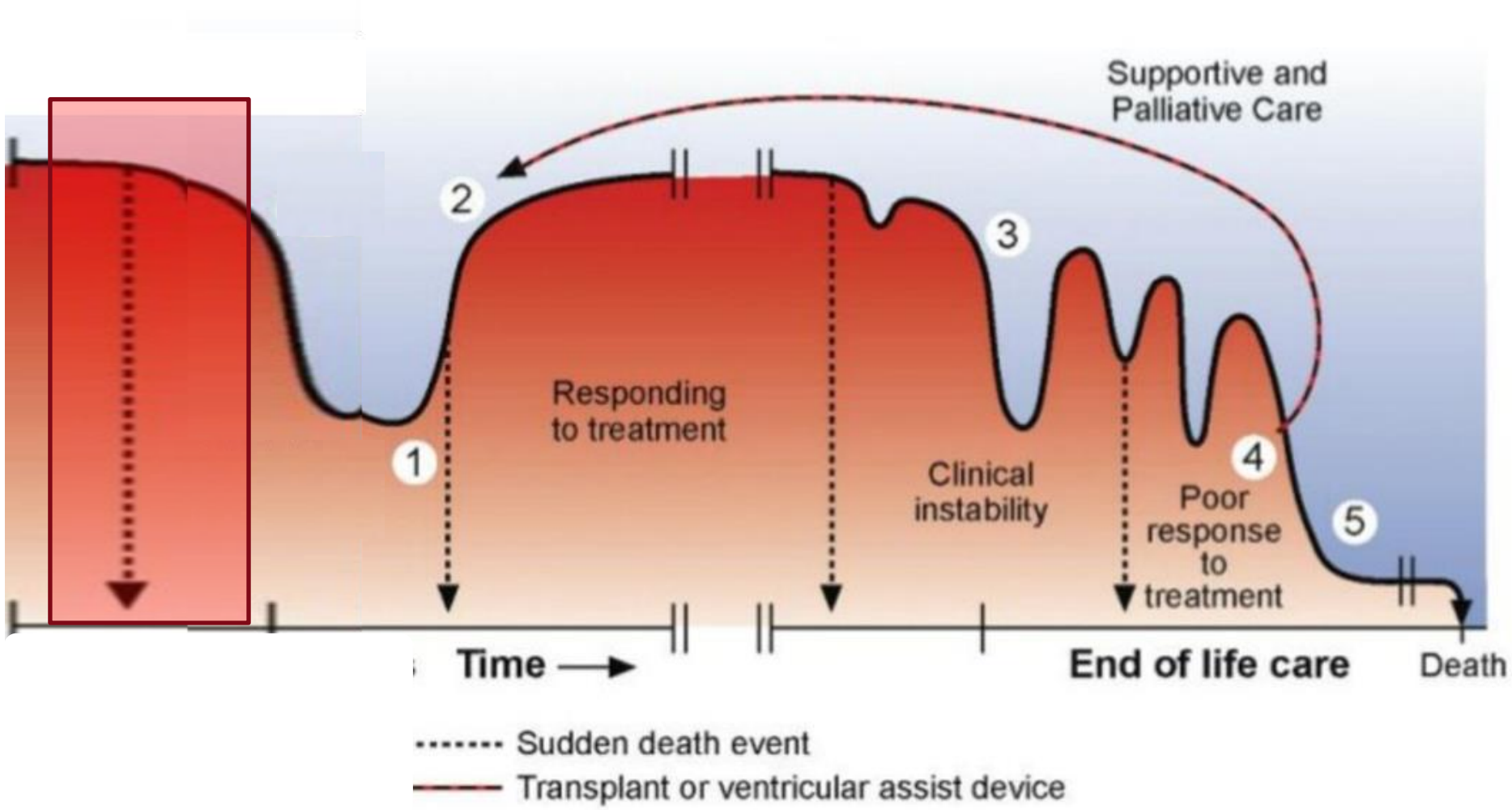
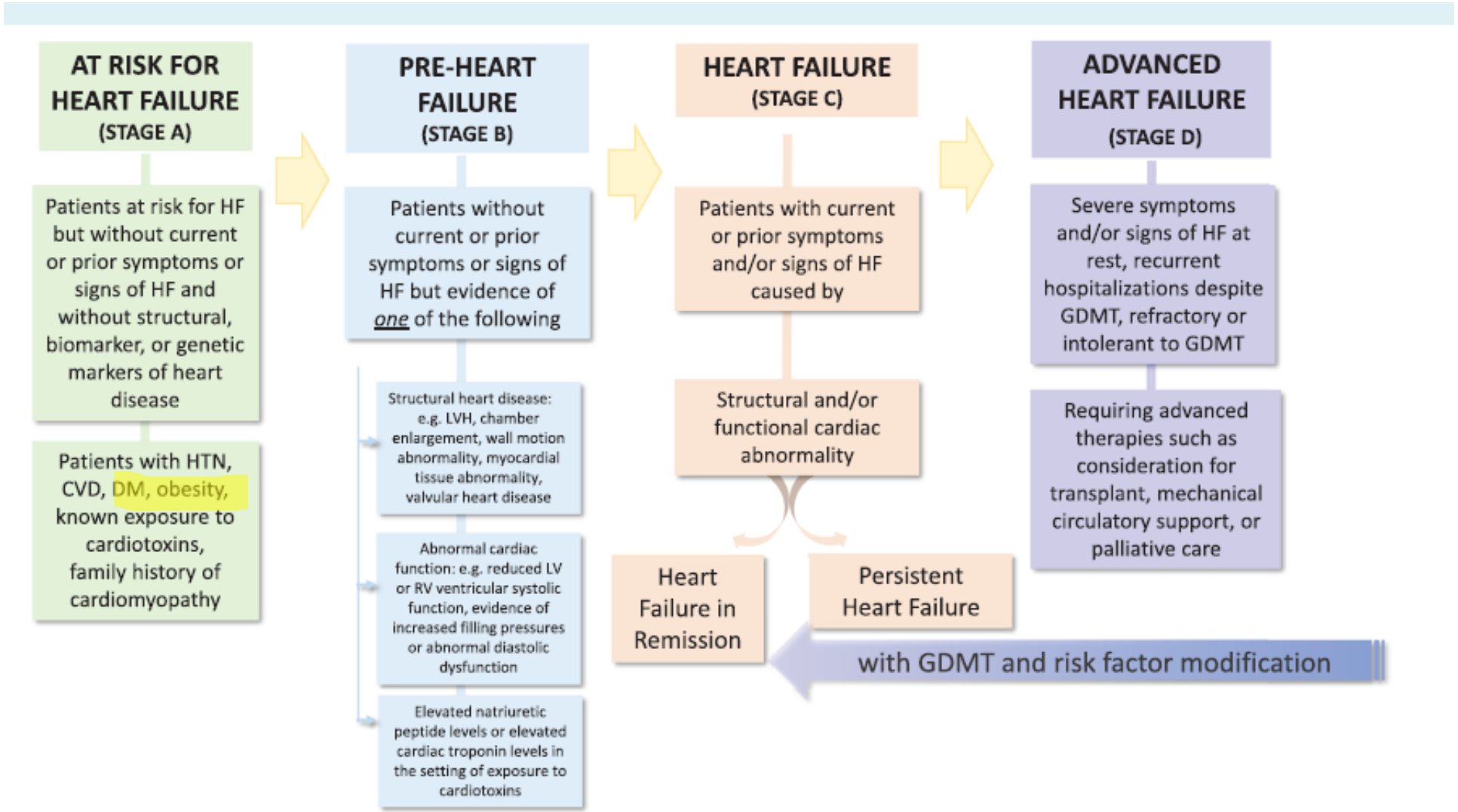
Worsening HF: a clinical consensus statement by the HFA of the ESC. European Journal of Heart Failure (2023) doi:10.1002/ejhf.2874

Heart Failure Trajectory- Can we act before?



Universal definition of HF



How to prevent HF in DM?

- Earlier strategies aimed at tight glycaemic control (i.e. targeting normal levels of glycosylated haemoglobin), mostly using insulin secretagogues and insulin -not effective in reducing risk of HF.
- More recent intensive glycaemic control - increased mortality (insulin secretagogues and insulin, rosiglitazone)
- Use of some medications (e.g. rosiglitazone) may increase the risk of HF

Prevention of HF in DM – iSGLT2

HFA Heart Failure Association

Table 4 Cardiovascular and renal outcome trials with SGTL2 inhibitors in patients with type 2 diabetes mellitus

Medication	Trial	Patients, *n*	Patient characteristics	Follow-up (mean or median), years	Primary outcome (HR, 95% CI; *P*-value)	HF hospitalization (HR, 95% CI; *P*-value)
Empagliflozin	EMPA-REG OUTCOME[21]	7020	Established CVD	3.1	3-point MACE[a] (0.86, 0.74–0.99, $P<0.001$ for non-inferiority; $P=0.04$ for superiority)	0.65, 0.50–0.85; $P=0.002$
Canagliflozin	CANVAS Program[22]	10 142	Established CVD (66%) CV risk factors (34%)	3.2	3-point MACE[a] (0.86, 0.75–0.97; $P<0.001$ for non-inferiority; $P=0.02$ for superiority)	0.67, 0.52–0.87
Dapagliflozin	DECLARE-TIMI 58[23]	17 160	Established CVD (41%) CV risk factors (59%)	4.2	Coprimary outcome: 3-point MACE[a] (0.93, 0.84–1.03; $P=0.17$) Coprimary outcome: CV death or HF hospitalization (0.83; 0.73–0.95; $P=0.005$)	0.73, 0.61–0.88
Ertugliflozin	VERTIS-CV[24]	8246	Established CVD	3.5	3-point MACE[a] 0.97 (0.85–1.11; $P<0.001$ for non-inferiority)	0.70, 95% CI 0.54–0.90; $P=0.006$
Canagliflozin	CREDENCE[25]	4401	Chronic kidney disease (eGFR, 30 to <90 mL per minute per 1.73 m^2 of body-surface area and ratio of albumin to creatinine >300–5000 mg/g)	2.6	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes (0.70, 0.59–0.82; $P<0.001$)	0.61, 0.47–0.80; $P<0.001$
Dapagliflozin	DAPA-CKD[26]	4304 (2906 with T2DM)	Chronic kidney disease (eGFR ≥25 and ≤75 mL/min/1.73 m^2; urinary albumin to creatinine ratio between ≥200 mg/g and ≤5000 mg/g)	2.4	Worsening kidney function (defined as >50% sustained decline in eGFR or onset of end-stage kidney disease), or death due to kidney disease or CVD) 0.61 (0.51–0.72; $P<0.001$)	0.71, 0.55–0.92; $P<0.001$

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SGLT2i – Prevention of HF

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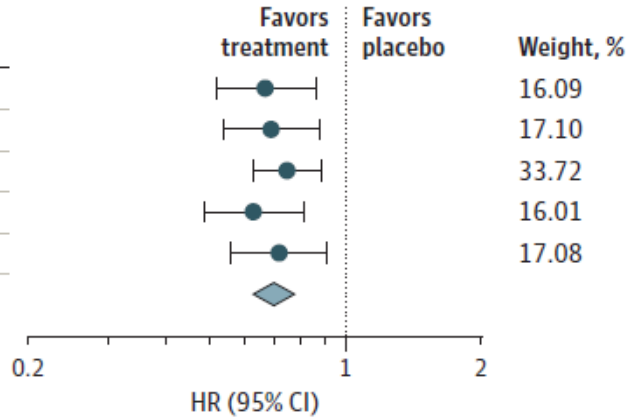
Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

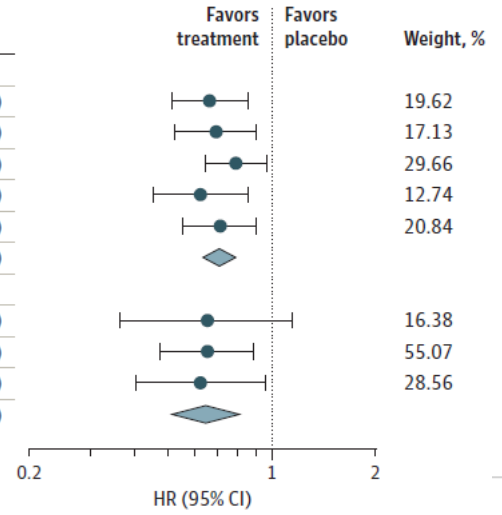
A Overall HHF

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)



B HHF by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.97; *df* = 4; *P* = .74; I^2 = 0.0%)					0.70 (0.62-0.78)
Patients without ASCVD					
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)



JAMA Cardiol. 2021;6(2):148-158.

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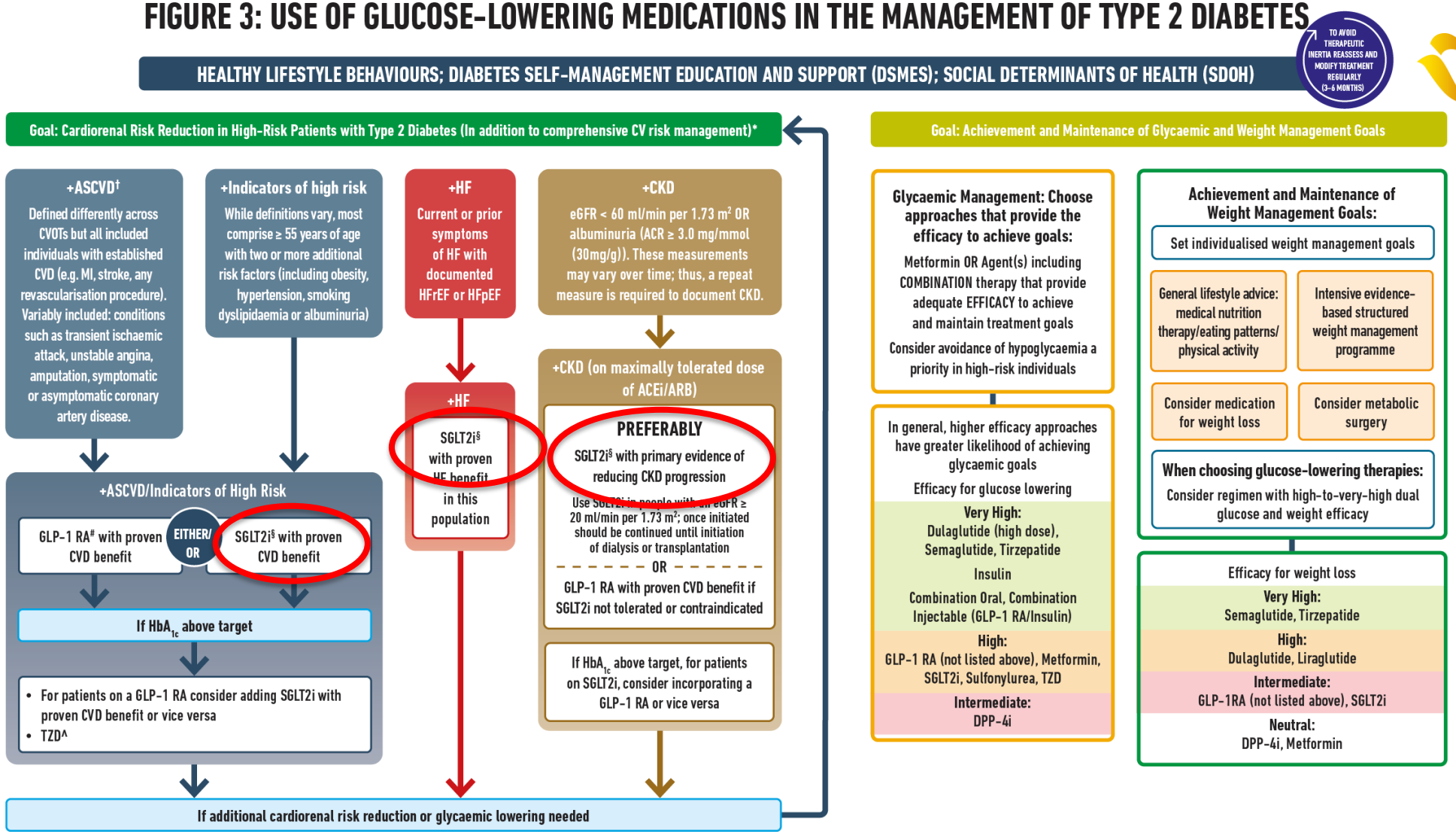
FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

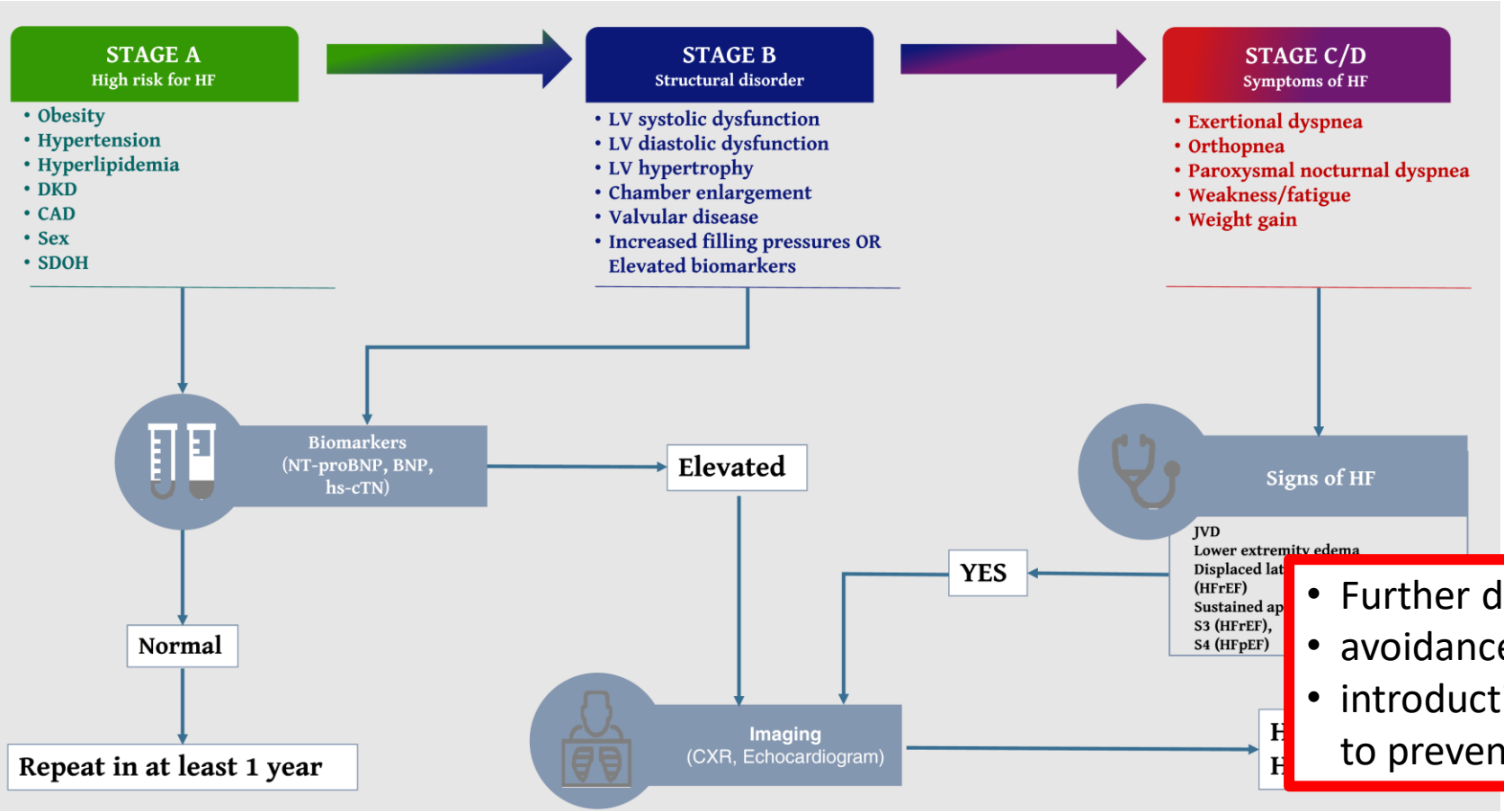
Prevention of HF in DM

- **PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial**
  - NT-proBNP >125 pg/ml
  - Primary endpoint -hospitalization/death due to cardiac disease
  - Accelerated up-titration of RAS antagonists and beta-blockers to maximum tolerated dosages is an effective and safe intervention for the primary prevention of cardiac events for diabetic patients pre-selected using NT-proBNP.

Hospitalization Due to	All	Control	Intensified	p Value
Any reason	135 (45%)	77 (51%)	58 (39%)	0.02
Cardiovascular event	25 (8%)	18 (12%)	7 (5%)	0.02
Cardiac event	19 (6%)	14 (9%)	5 (3%)	0.03
Heart failure	8 (3%)	7 (5%)	1 (1%)	0.003

J Am Coll Cardiol . 2013 Oct 8;62(15):1365-72

ADA – screening, BM, thresholds



BNP>50 pg/mL
NT-proBNP >125 pg/mL
hs troponin >99th percentile

- Further diagnostic studies,
- avoidance treatments that might increase HF risk,
- introduction of therapies with proven usefulness to prevent HF

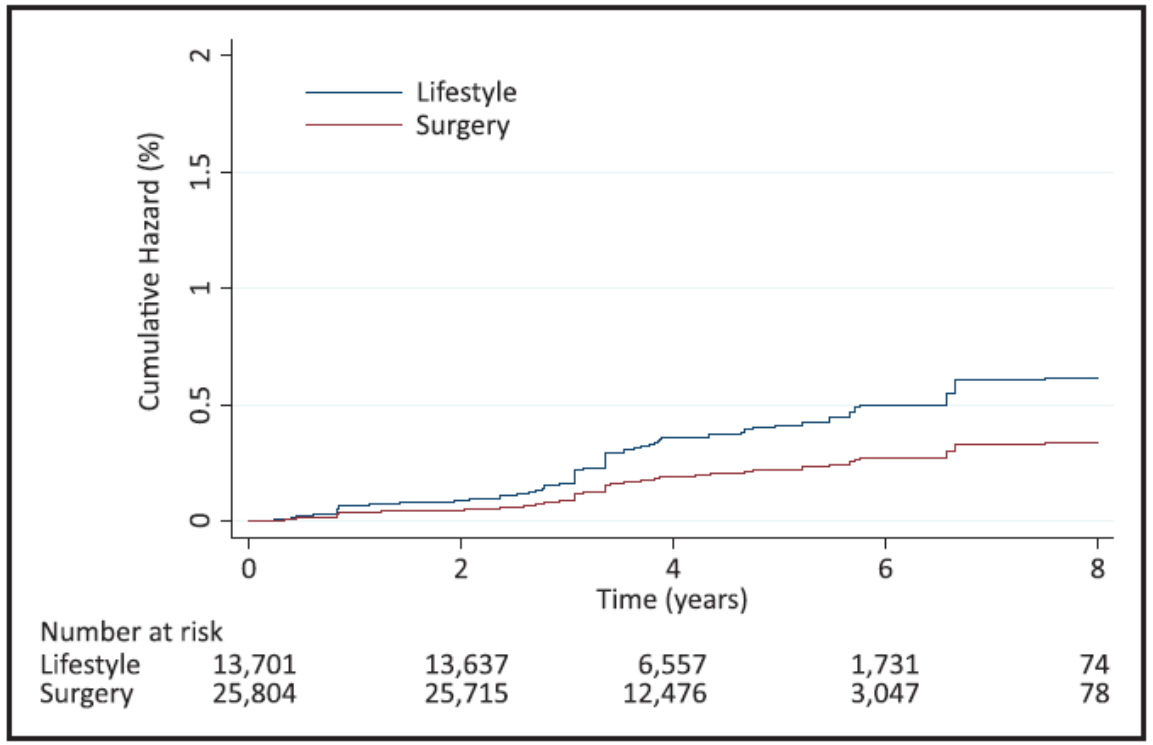
Diabetes Care. 2022;45(7):1670-1690. doi:10.2337/dci22-0014

Obesity

- **Risk of HF development increases by 5–7% with each increment of 1 kg/m2 in BMI**
- **C**ontribution of obesity (BMI > 30 kg/m2) to the development of HFpEF is greater than for HFrEF, body weight is a risk factor in both scenarios
- In a population study from Rochester,Minnesota, obesity was present in **20.5% of newly diagnosed patients with HF during 1985 to 1990** compared with **29.5% from 1997 to 2002**
- The population attributable risk (PAR) of obesity for incident HF was estimated at 12%.
- **Modest weight reductions of 5–10% improve cardiovascular risk factors, with greater weight loss bringing about greater benefits.**

Kenchaiah S, et al. N Engl J Med 2002;347:305–313; European Journal of Preventive Cardiology (2022) 29, 275–300;

Preventing HF in Obesity -Bariatric surgery



Cumulative hazard of heart failure in individuals treated with lifestyle or gastric bypass surgery.

Swedish nationwide registry of people treated with a structured intensive lifestyle program and the **Scandinavian Obesity Surgery Registry**

25 804 individuals were treated with gastric bypass surgery and 13 701 with lifestyle modification.

Gastric bypass surgery was associated with a nearly **halved incidence of heart failure** compared with an intensive lifestyle modification

Circulation. 2017;135:1577–1585.

Weight loss achieved with anti-obesity medications

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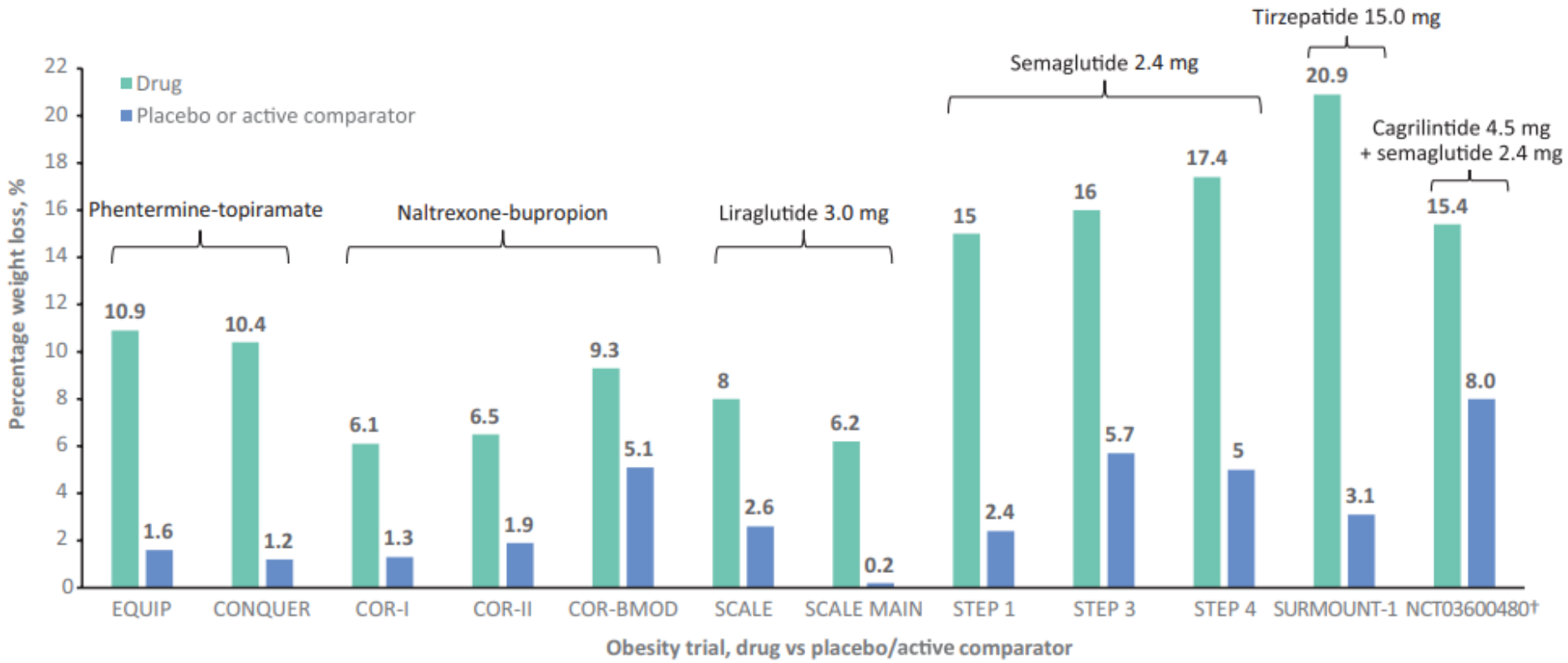
Fig. 1



Ryan DH, et al. Cardiovasc Endocrinol Metab. 2023 Feb 7;12(1):e0279;

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Preventing HF in Obesity

SELECT Trial- semaglutide 2.4 mg versus placebo for cardiovascular risk reduction in overweight/obesity

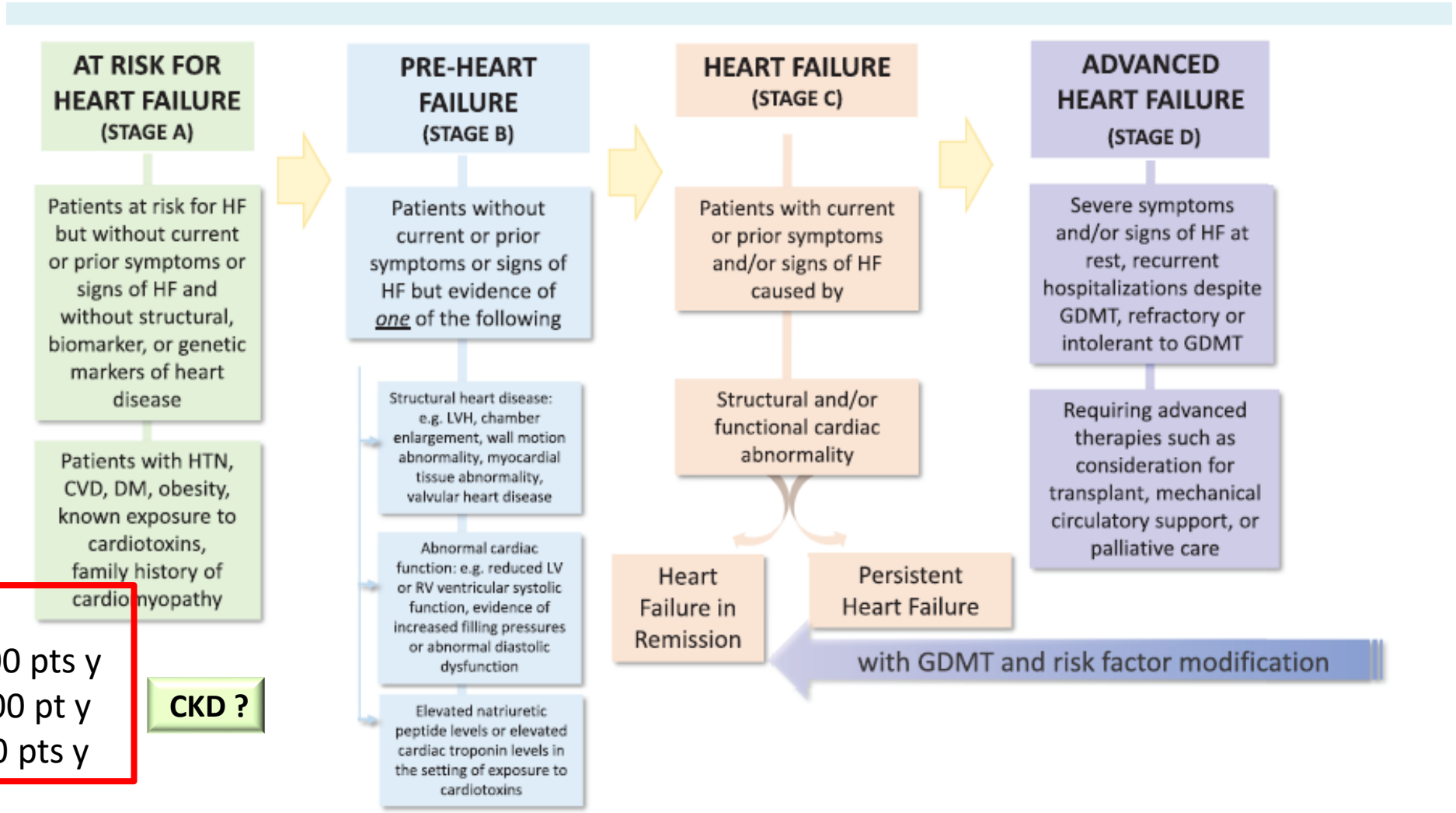
- **17 500 pts with CVD in the absence of T2D or HbA1c >6.5%.**
- **It is the first dedicated CVOT for an obesity treatment that seeks to establish superiority in the prevention of MACE**
- **Completed by September, 2023**

SURMOUNT-MMO - A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity

- **15000 participants with overweight/obesity with CVD or risk factors**
- **Recruiting**
- **Completed by 2027**

SELECT. Am Heart J 2020; 229:61–69; ClinicalTrials.gov Identifier: NCT05556512

Universal definition of HF



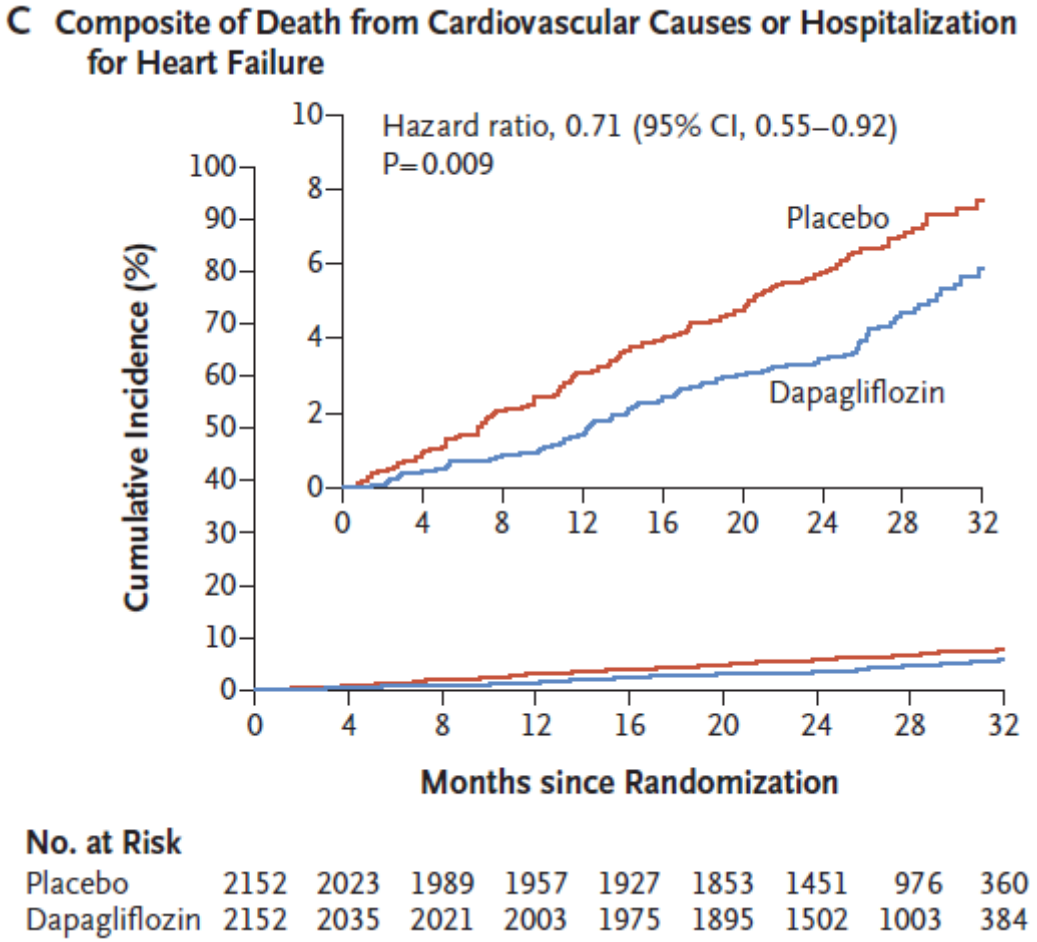
CKD ?

HHF	
EMPAREG-Out	1,45/100 pts y
DECLARE	0,85/100 pt y
DAPA-CKD	1,6/100 pts y

Prevention of HF in CKD

DAPA-CKD trial

- 4304 pts,
- eGFR of 25 to 75 ml/min/1.73 m2 BSA
- Urinary albumin-to-creatinine ratio of 200 to 5000
- Dapagliflozin 10 mg od or placebo.
- Primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.



DAPA-CKD. N Engl J Med 2020;383:1436-46.

Prevention of HF in CKD

DAPA-CKD trial

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	P Value for Interaction
Primary outcome						
eGFR decline ≥50%, ESKD, or kidney or CV death						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
Without CV disease	106/1339	175/1355	4.0	6.7	0.61 (0.48, 0.78)	0.90
With CV disease	91/813	137/797	5.5	8.7	0.61 (0.47, 0.79)	
Secondary outcomes						
eGFR decline ≥50%, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
Without CV disease	93/1339	154/1355	3.6	5.9	0.61 (0.47, 0.79)	0.29
With CV disease	49/813	89/797	2.9	5.6	0.49 (0.34, 0.69)	
CV death or hospitalization for heart failure						
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
Without CV disease	24/1339	36/1355	0.8	1.3	0.67 (0.40, 1.13)	0.88
With CV disease	76/813	102/797	4.3	6.1	0.70 (0.52, 0.94)	
All-cause death						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
Without CV disease	33/1339	53/1355	1.1	1.8	0.63 (0.41, 0.98)	0.71
With CV disease	68/813	93/797	3.8	5.4	0.70 (0.51, 0.95)	
Prespecified exploratory CV outcomes						
CV death, myocardial infarction, or stroke						
Overall	132/2152	143/2152	2.9	3.1	0.92 (0.72, 1.16)	
Without CV disease	41/1339	50/1355	1.4	1.7	0.83 (0.55, 1.25)	0.61
With CV disease	91/813	93/797	5.2	5.5	0.94 (0.71, 1.26)	
First heart failure hospitalization						
Overall	37/2152	71/2152	0.8	1.6	0.51 (0.34, 0.76)	
Without CV disease	4/1339	13/1355	0.1	0.5	0.31 (0.10, 0.94)	0.35
With CV disease	33/813	58/797	1.9	3.5	0.54 (0.35, 0.82)	

Circulation. 2021;143:438–448.

Prevention of HF in DM T2 and CKD

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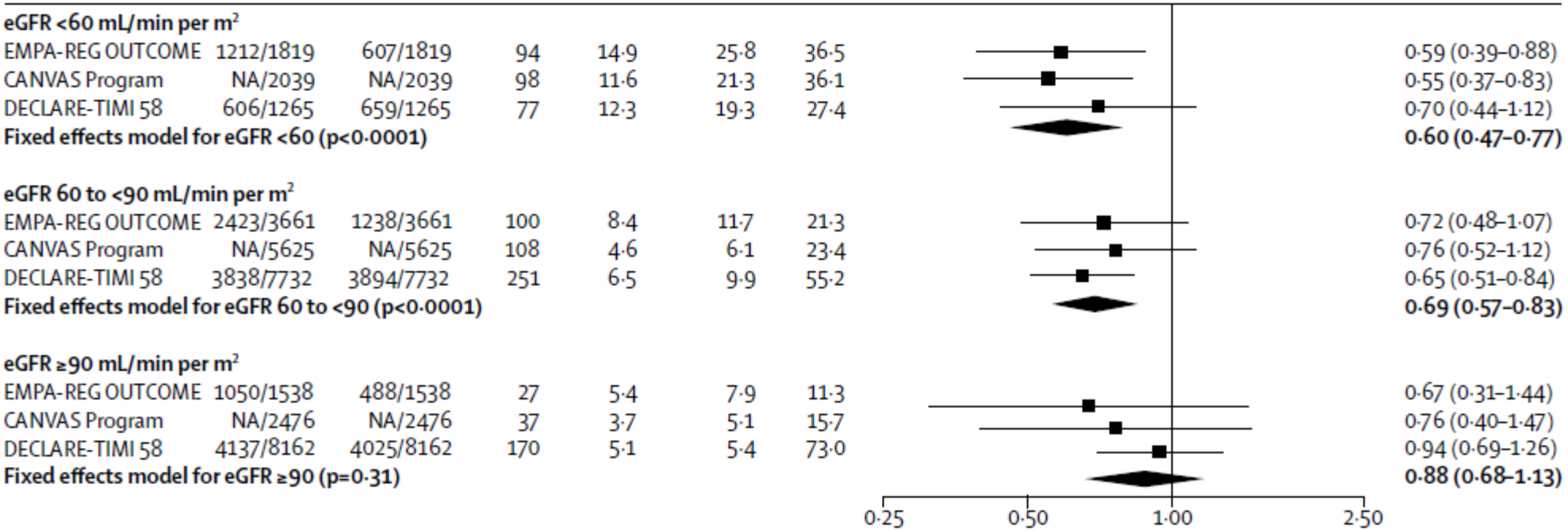
Meta-analysis of iSGLT2 in DM

hospitalisation for heart failure



Zelniker TA, et al. Lancet. 2019 Jan 5;393(10166):31-39

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Finerenone Reduces Risk of Incident HF in Patients With CKD and Type 2 DM: Analyses From the FIGARO-DKD Trial

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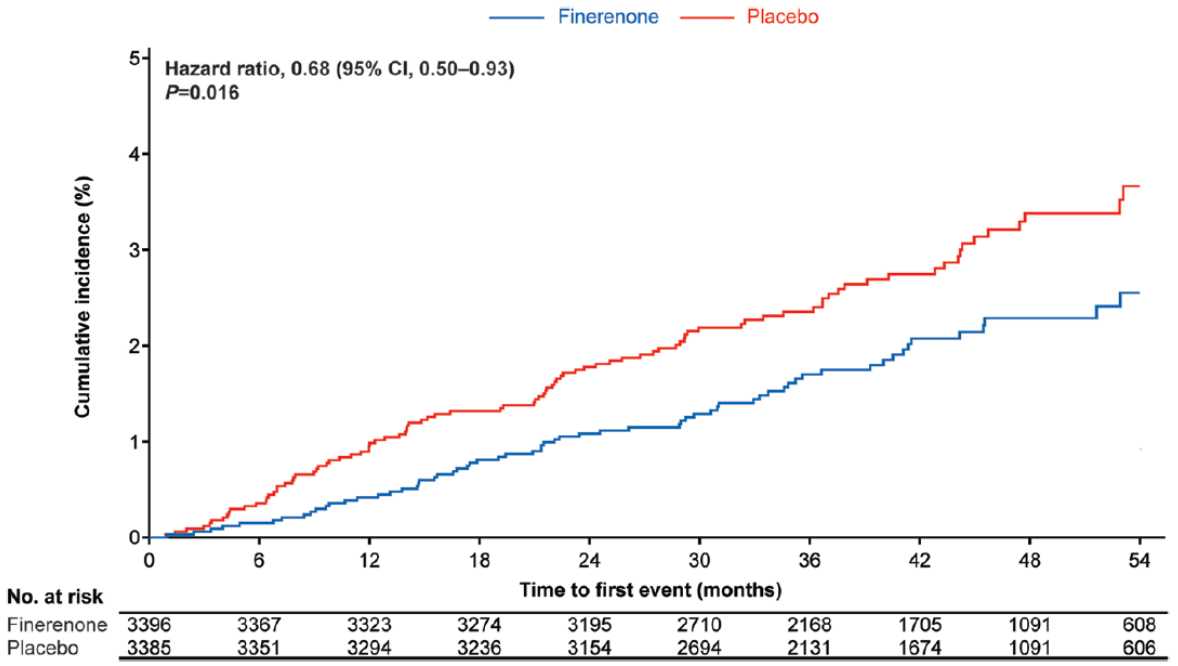
Finerenone -a selective, nonsteroidal mineralocorticoid receptor antagonist

FIDELIO-DKD -in CKD and DM T2, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.

FIGARO-DKD - Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease
7352 patients

Improved CV outcomes in patients with albuminuric CKD and type 2 diabetes.



Kaplan-Meier estimate of **time to new-onset HF** (first hospitalization for HF in patients without a history of HF at baseline).

Circulation. 2022;145:437–447.

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Impact HF Trajectory

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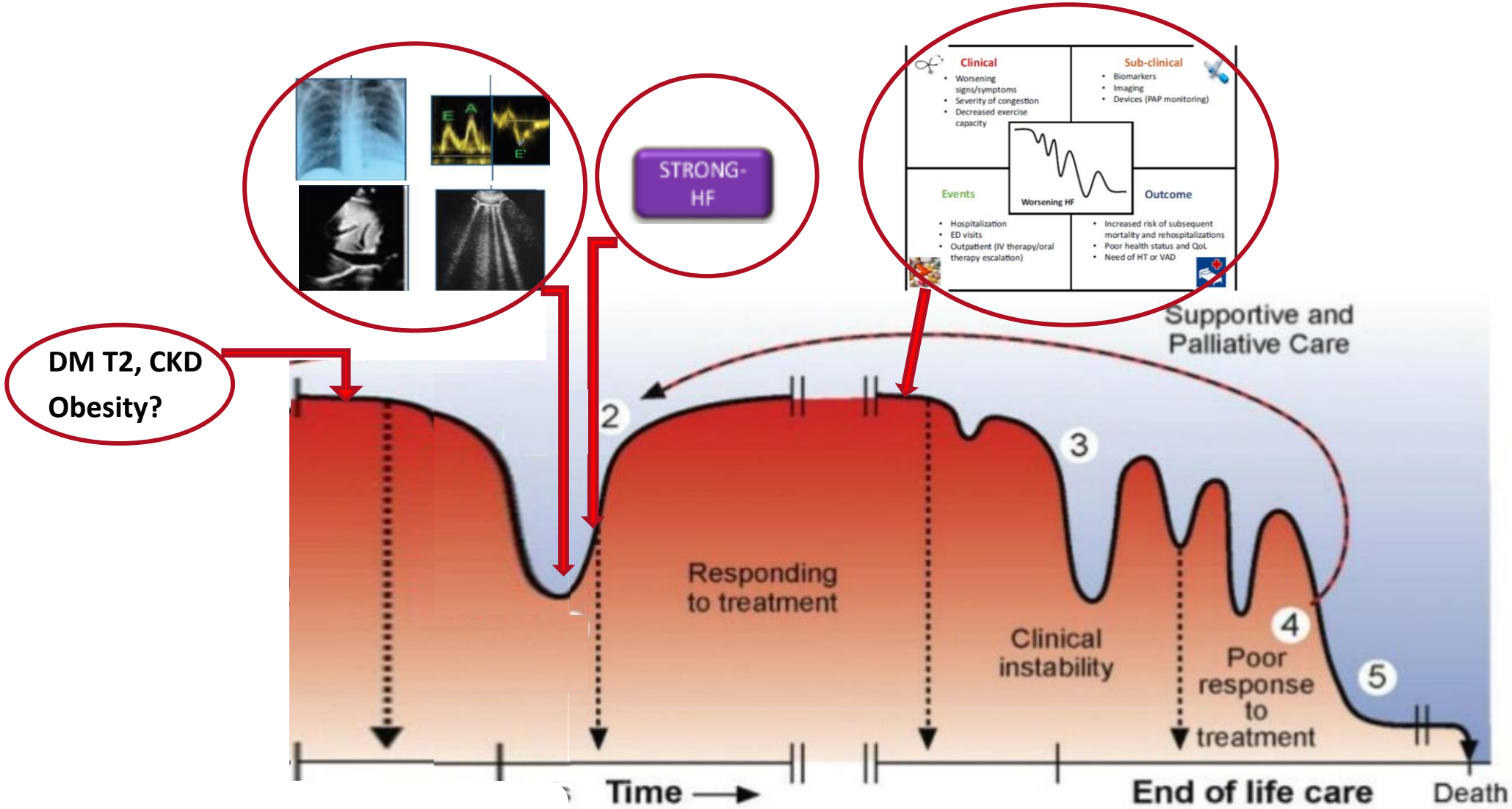

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HFpEF Profiling to Guide Therapy

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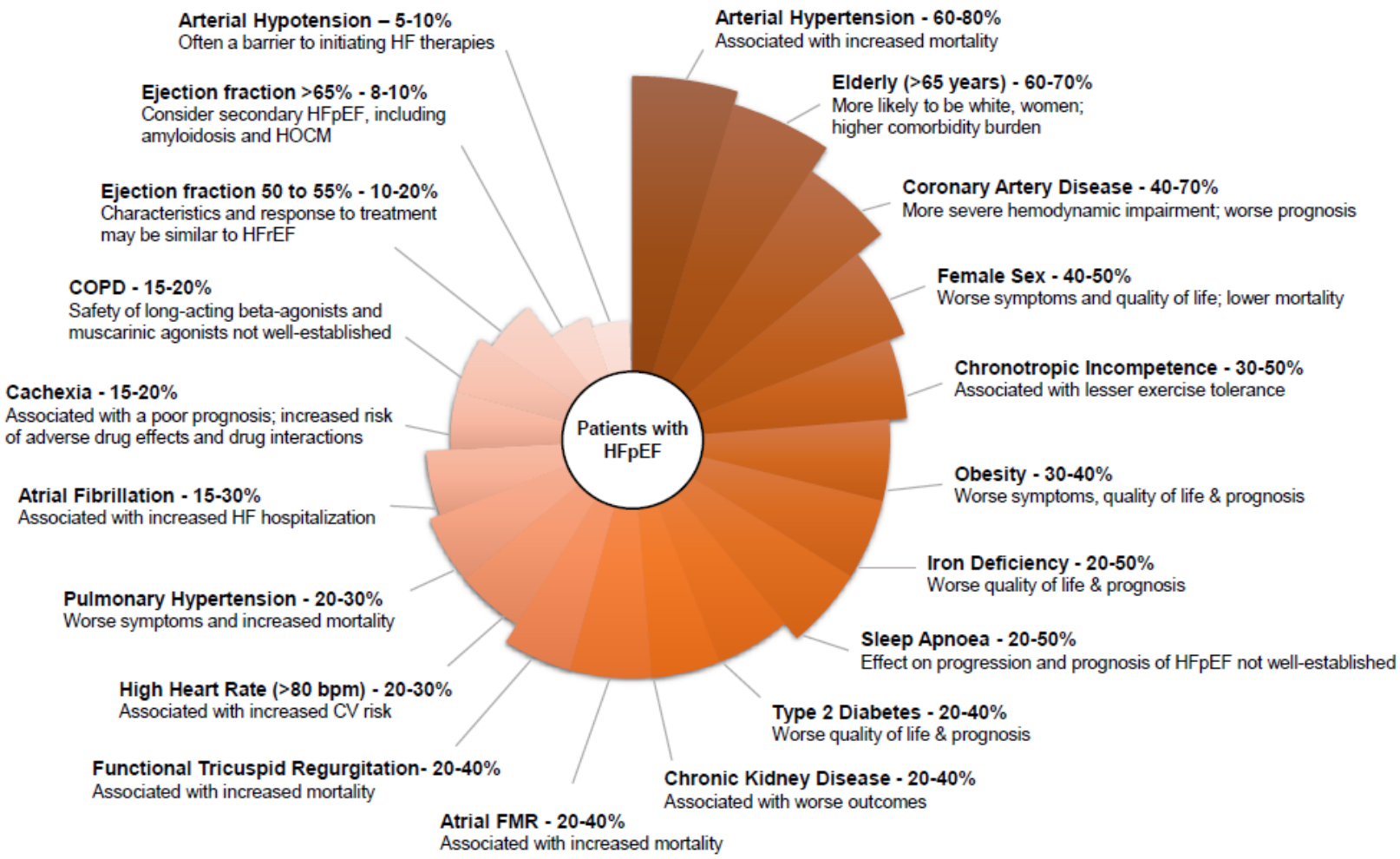
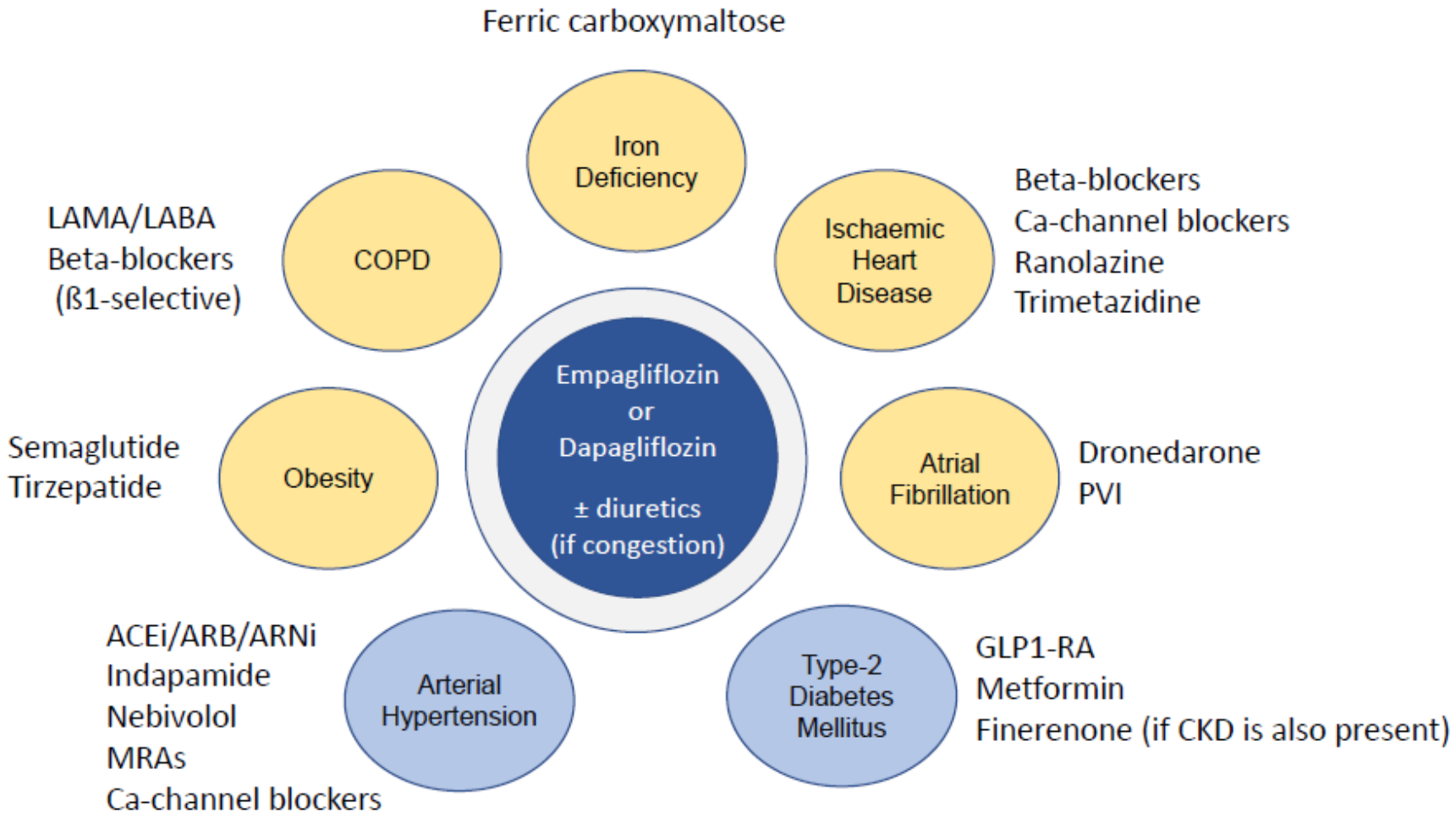


Patient Phenotype Profiling in Heart Failure with Preserved Ejection Fraction to Guide Therapeutic Decision Making . A Scientific Statement of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the ESC, and the European Society of Hypertension (ESH)

ESC

Pt profiling in HFpEF and therapeutic considerations

HFA Heart Failure Association



Patient Phenotype Profiling in Heart Failure with Preserved Ejection Fraction to Guide Therapeutic Decision Making . A Scientific Statement of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the ESC, and the European Society of Hypertension (ESH)

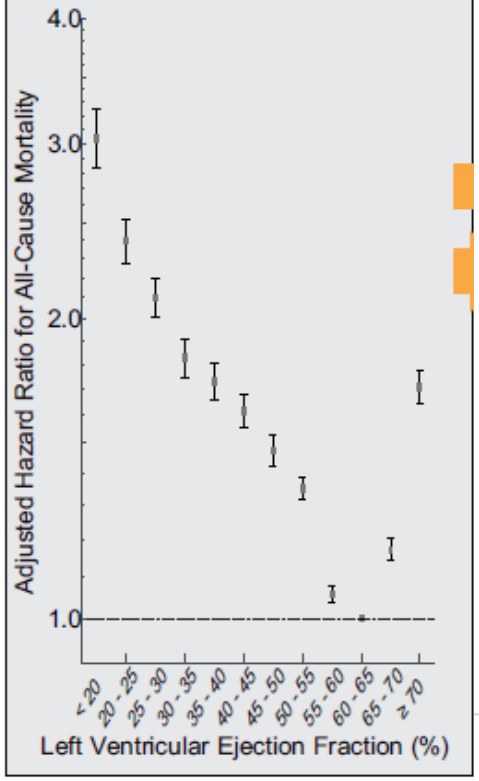
ESC

Routinely reported EF and mortality in clinical practice- where does the nadir of risk lie?

HFA Heart Failure Association

Physician-reported LVEF from 403,977 echocardiograms (203,135 unique patients)

Increased risk of mortality at both low and high LVEF



Increased risk remained after:

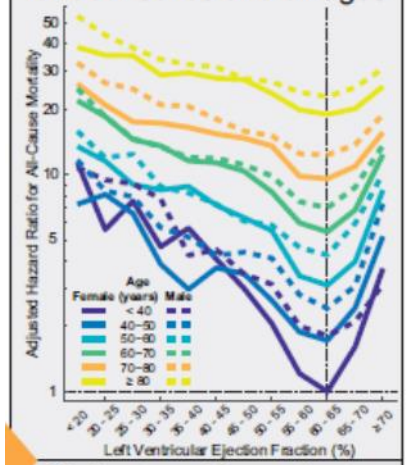
Analyzing only one echocardiogram per patient

Removing effect of serious acute illness by excluding mortality within 90 days

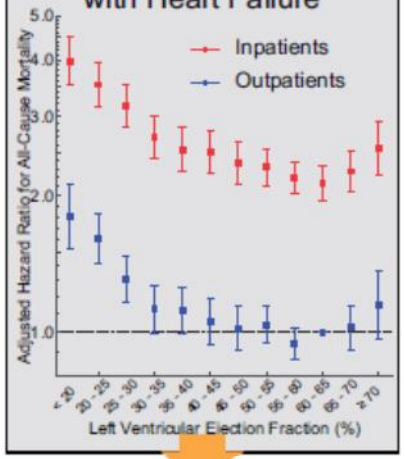
Including additional confounders associated with pathologically high LVEF

(Heart rate, blood pressures, body temperature, LV wall thickness, LV volumes, mitral regurgitation, anemia, hyperthyroidism)

Similar u-shaped trend for both sexes and all ages



Similar trend for patients with Heart Failure



Suggests new phenotypes notable for supranormal LVEF

ESC

Wehner et al. European Heart Journal (2020) 41, 1249–1257

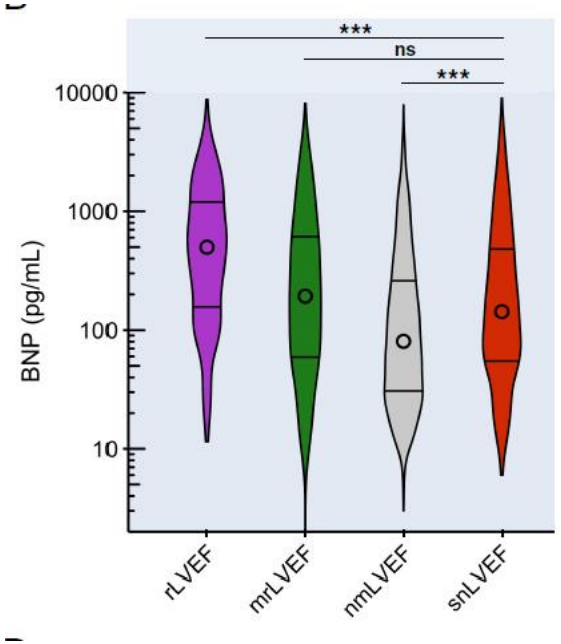
ESC European Society of Cardiology
European Journal of Heart Failure (2022)
doi:10.1002/ejhf.2482
RESEARCH ARTICLE

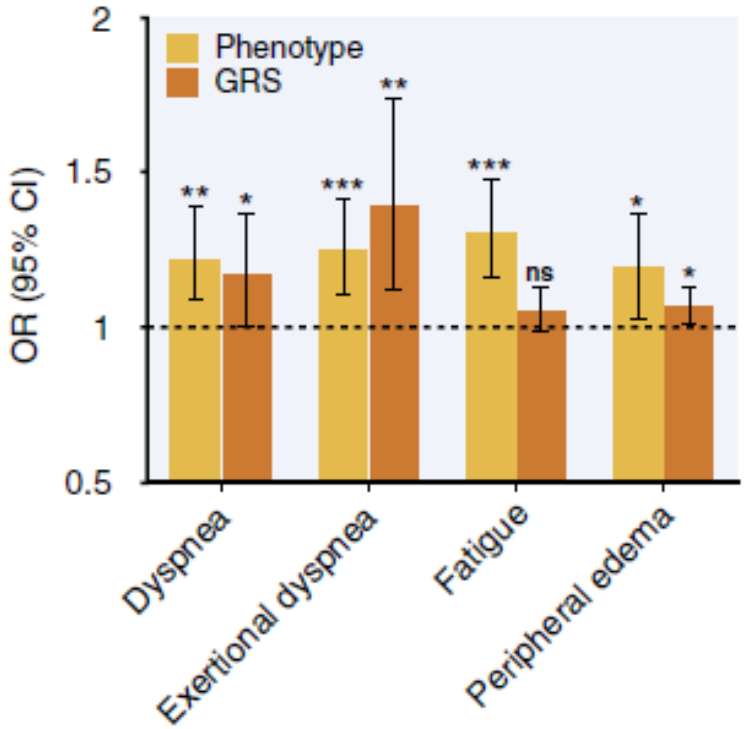
HFA Heart Failure Association

Genetic and phenotypic profiling of supranormal ejection fraction reveals decreased survival and underdiagnosed heart failure

Iain S. Forrest[1,2,3,4], Ghislain Rocheleau[1,4], Shantanu Bafna[1,4], Edgar Argulian[5], Jagat Narula[5], Pradeep Natarajan[6,7], and Ron Do[1,3,4]*

- 486 754 individuals recruited as volunteers from the UK Biobank and outpatients from the Mount Sinai BioMe Biobank
- 30 557 individuals had cardiac imaging data





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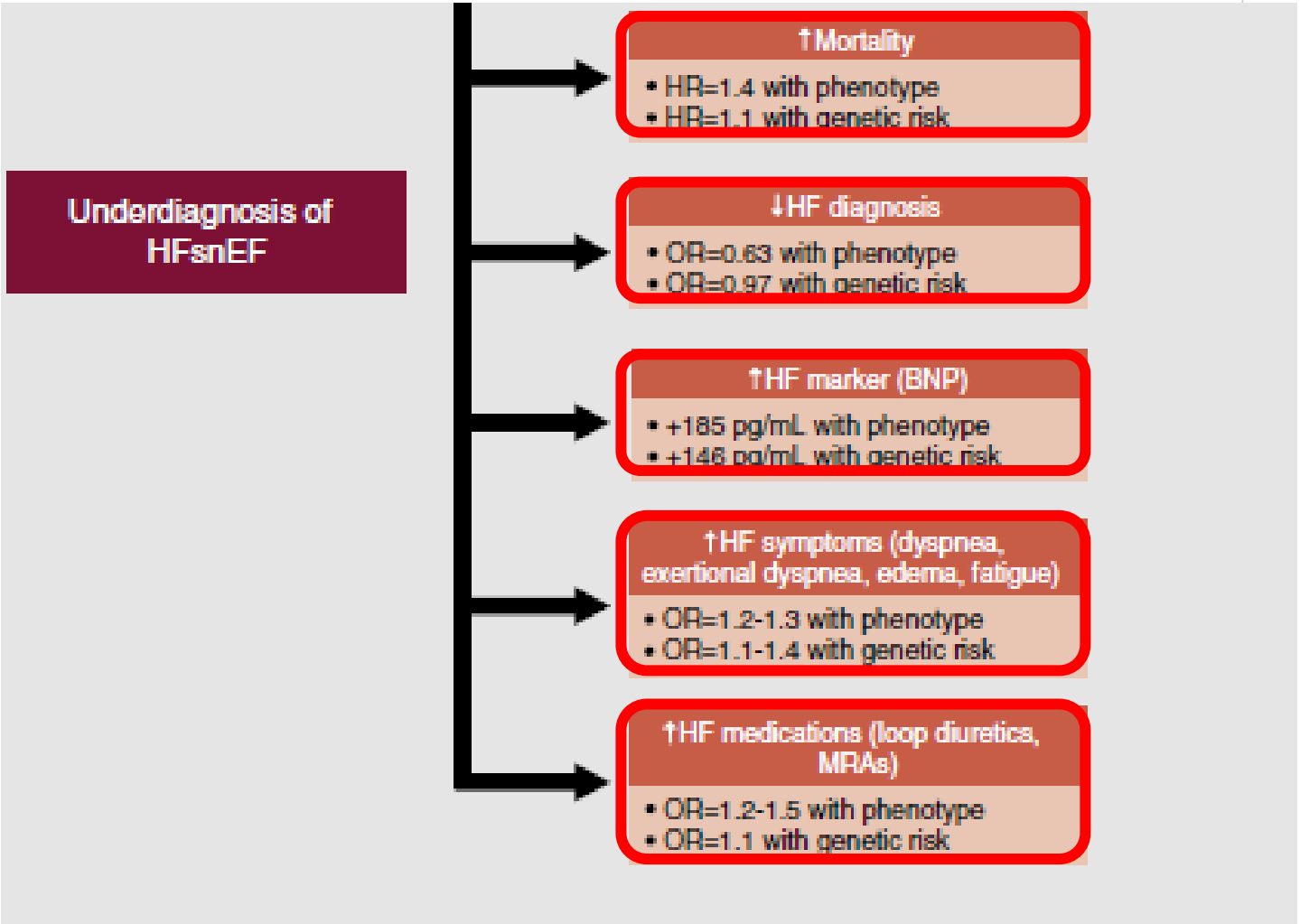
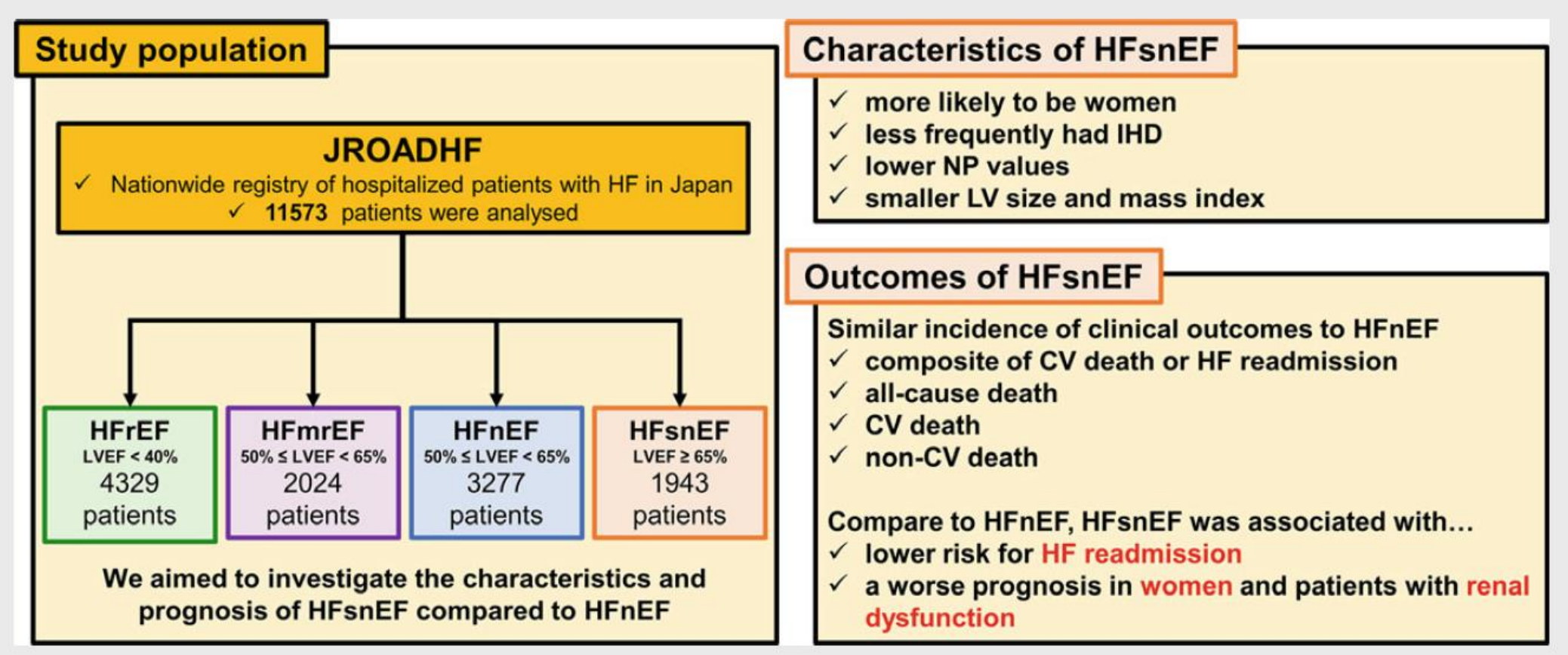
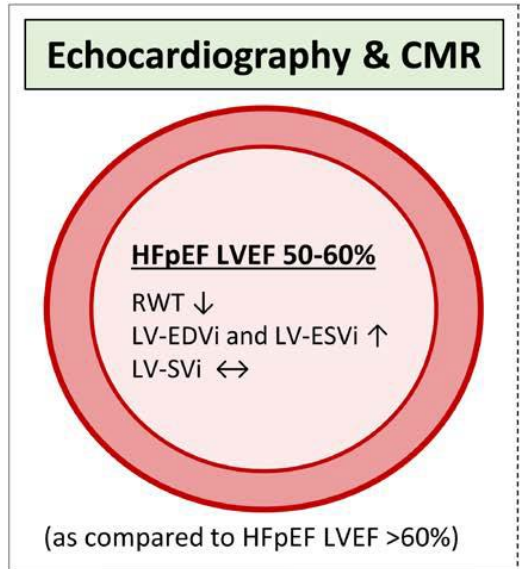


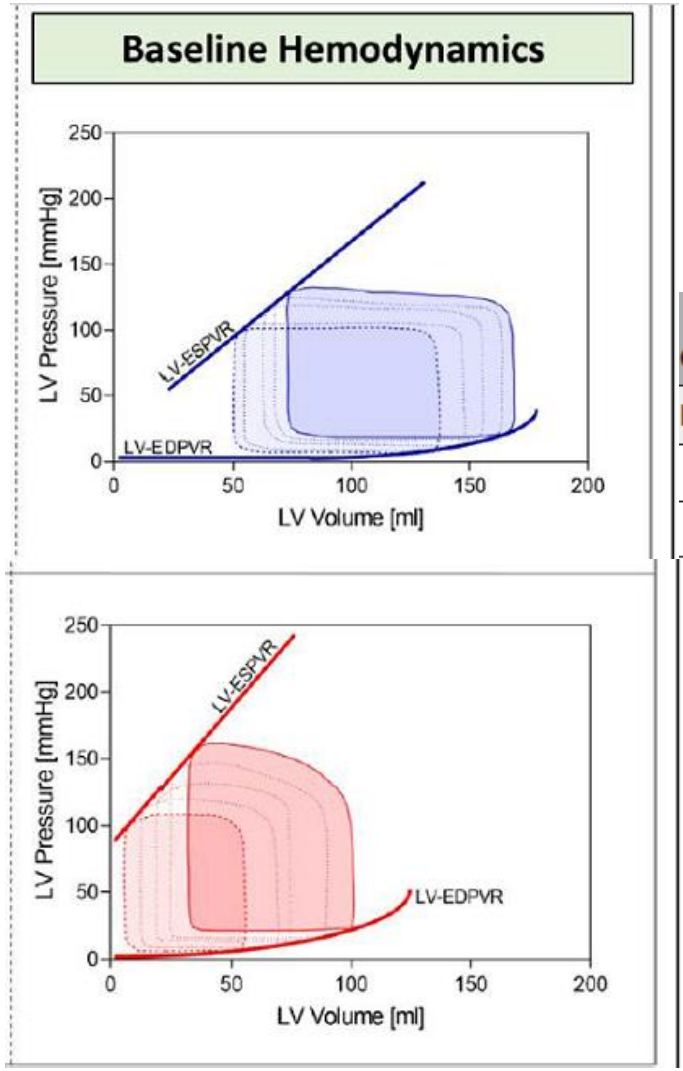
HF supra-normal ejection fraction: Insight from the JROADHF study



Horiuchi Y, et al. Eur J Heart Fail. 2023 May 16.

Characteristics of Heart Failure With Preserved Ejection Fraction Across the Range of LVEF

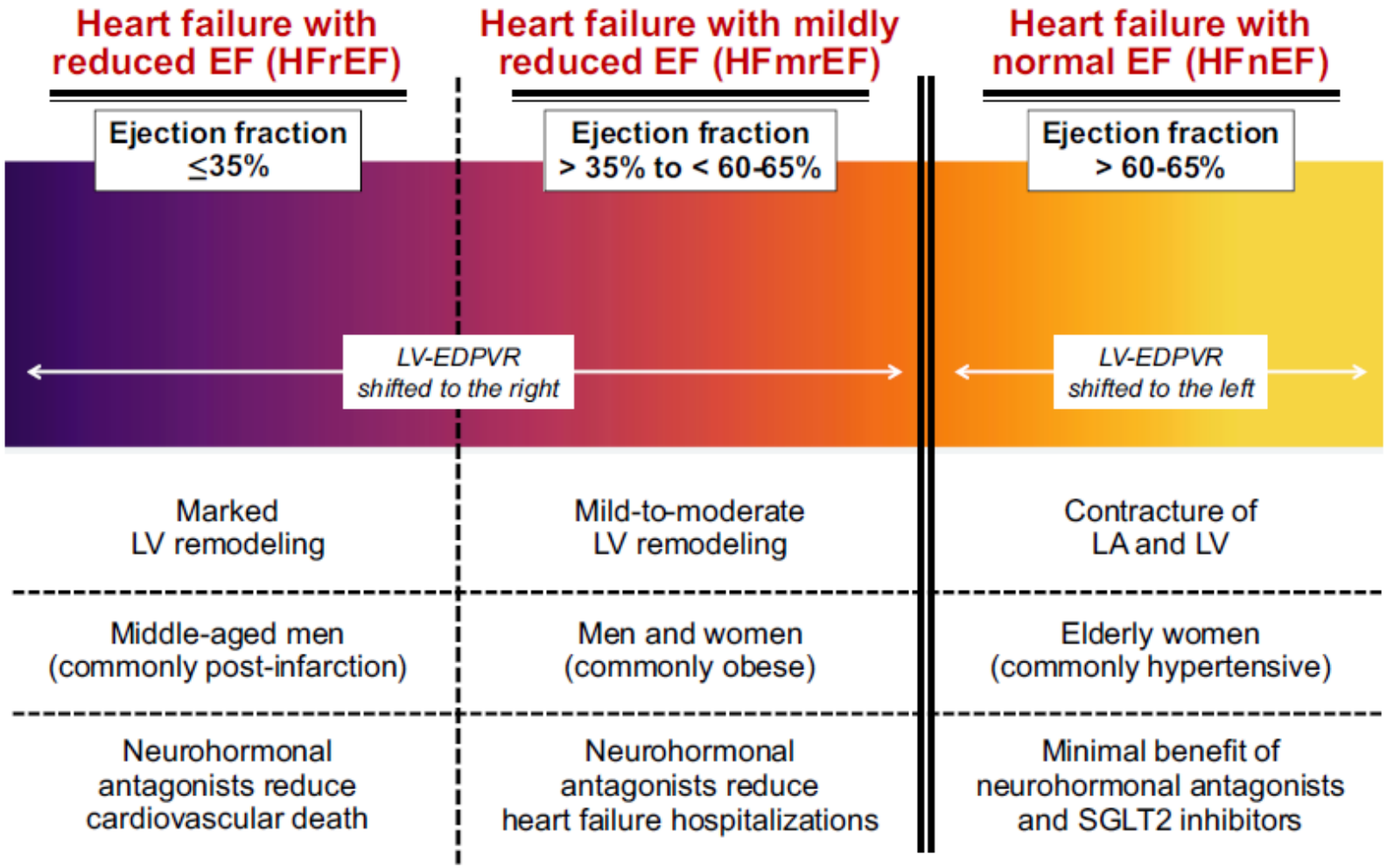




Characteristics	LVEF 50% to 60% (n=21)	LVEF >60% (n=35)
Baseline characteristics		
Age, y	69 (64, 73)	72 (68, 78)*
Female sex	12 (57)	28 (80)
Body mass index, kg/m²	32.6 (27.1, 35.2)	31.6 (27.1, 33.7)
Body surface area, m²	2.1 (1.8, 2.2)	2.0 (1.9, 2.0)
H_2FPEF score†	6 (4.5, 8)	6 (4, 7)

Rosch S, et al. Circulation. 2022;146:506–518.

Reclassification of heart failure based on LV remodelling and contracture phenotypes



Packer M. Eur J Heart Fail. 2023 Apr 3

Take home messages

- **It is possible to impact HF trajectory**
  - Prevention of HF in some high risk pts
  - Profit from a HHF to implement GDMT (4 pillars at discharge, target dose at 2 weeks)
  - Careful evaluation of congestion before discharge to reduce risk (NP, Echo –IVC, IJV, LUS)
  - Careful evaluation of congestion in ambulatory pts to prevent WHF
- **Profile HFpEF pts to implement therapy**
- **HF supra normal EF – a new phenotype?**