Optimization in Management of Chronic Heart Failure

Dr Thet Lel Swe Aye

Associate Professor/Senior Consultant Cardiologist

Department of Cardiology

Yangon General Hospital

Disclosure

Nothing to declare

Outline

- Introduction
- How to diagnose heart failure
- Optimization of guideline directed medical therapy (GDMT) with clinical evidences
  - For heart failure with reduced LVEF (HFrEF)
  - For heart failure with preserved LVEF (HFpEF)
- Indication for Cardiac Implantable Electronic Devices (CIEDs) in HErEF
- Holistic care

Introduction

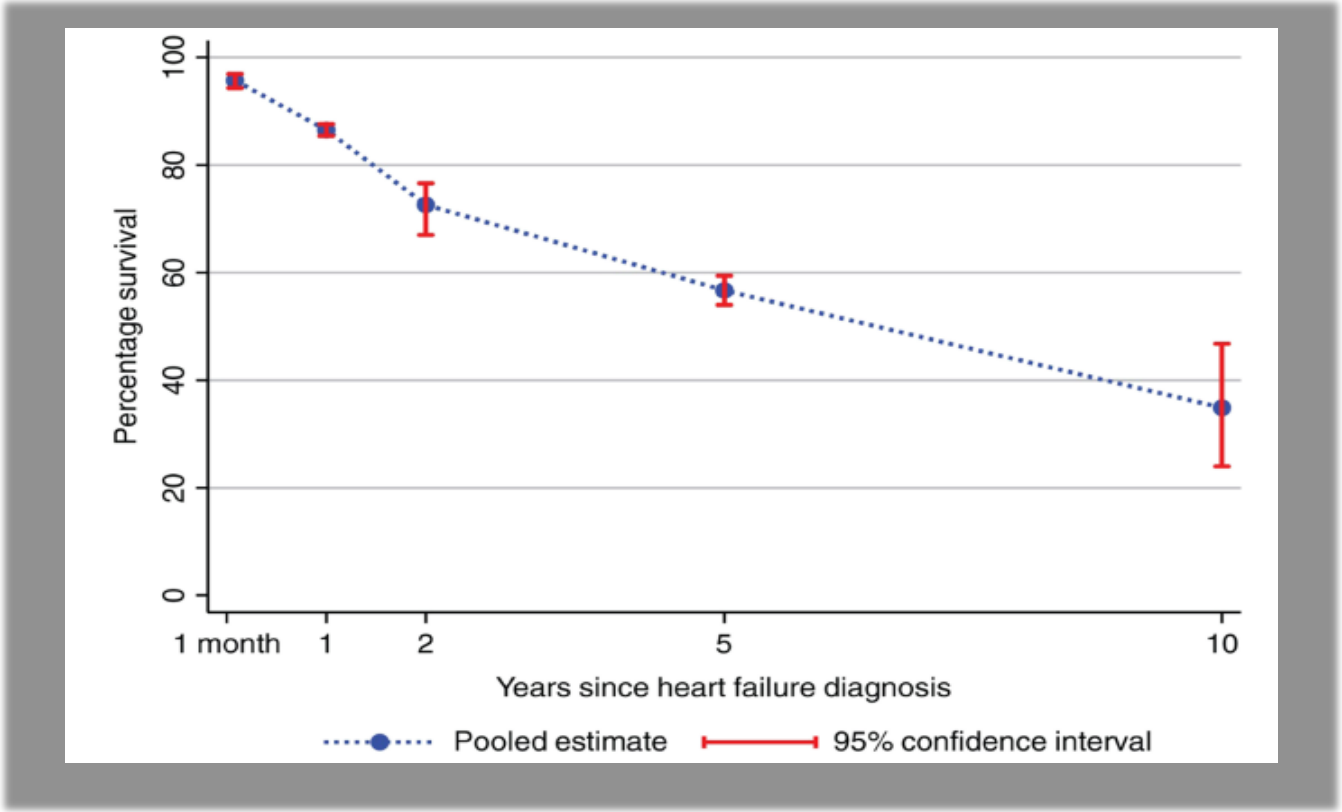
- Heart failure is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood.

- The true prevalence of heart failure in **Asia Pacific region** is suggested to range from **1.3% to 6.7%**, translating to an average of **4 cases** of heart failure for **every 100 people** in the region.

- Registry and epidemiological data indicate that HF patients in the Asia-Pacific are **younger** and have **more severe signs and symptoms** compared with their counterparts in Western countries.

- In the Asia-Pacific region, heart failure (HF) becomes a public health problem because of its high prevalence, huge socioeconomic burden and poor outcome.

Combined survival rates for people with heart failure over time

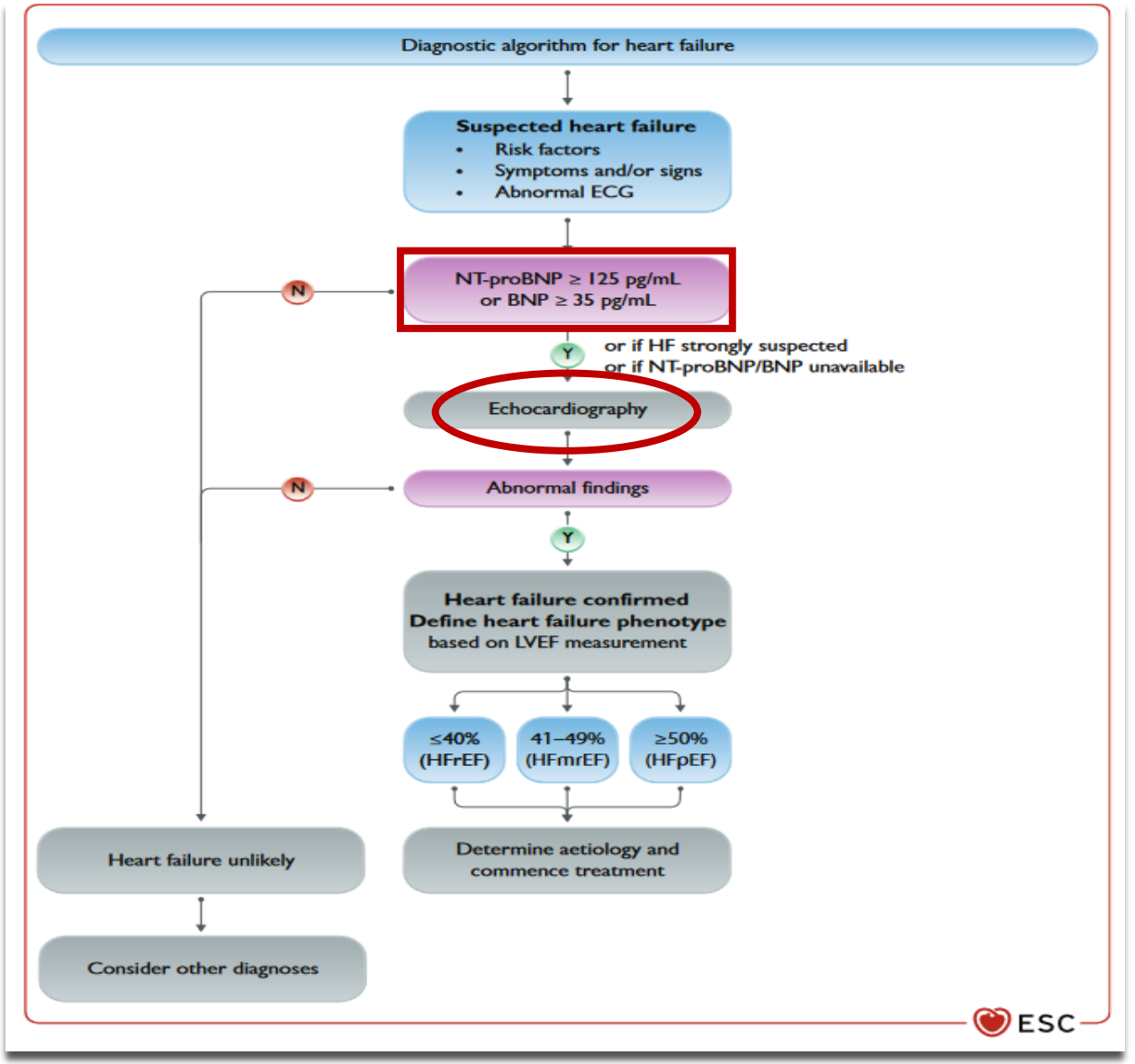


Ref : Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail 2019; 21:1306–1325.

ACC/ AHA Heart Failure Stage and NYHA class

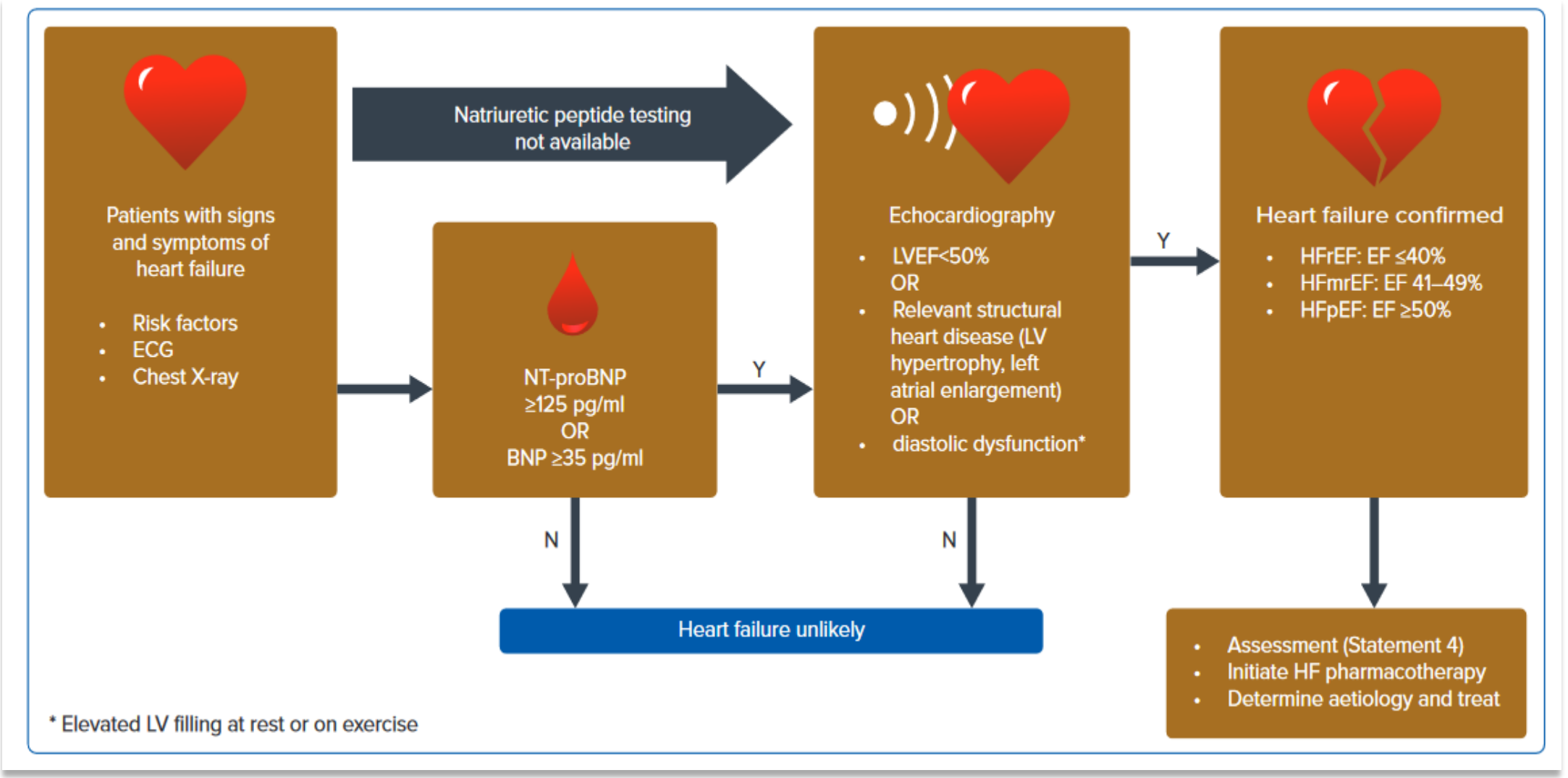
ACC/AHA Heart Failure Stage	NYHA Class
A. at risk for developing HF, without signs and symptoms	
B. asymptomatic structural heart disease	I. asymptomatic
C. symptomatic or previously symptomatic structural heart disease	1. I. asymptomatic 2. II. symptomatic with moderate exertion 3. III. symptomatic with minimal exertion 4. IV. symptomatic at rest
D. refractory heart failure requiring advanced interventions	IV. symptomatic at rest

The diagnostic algorithm of heart failure

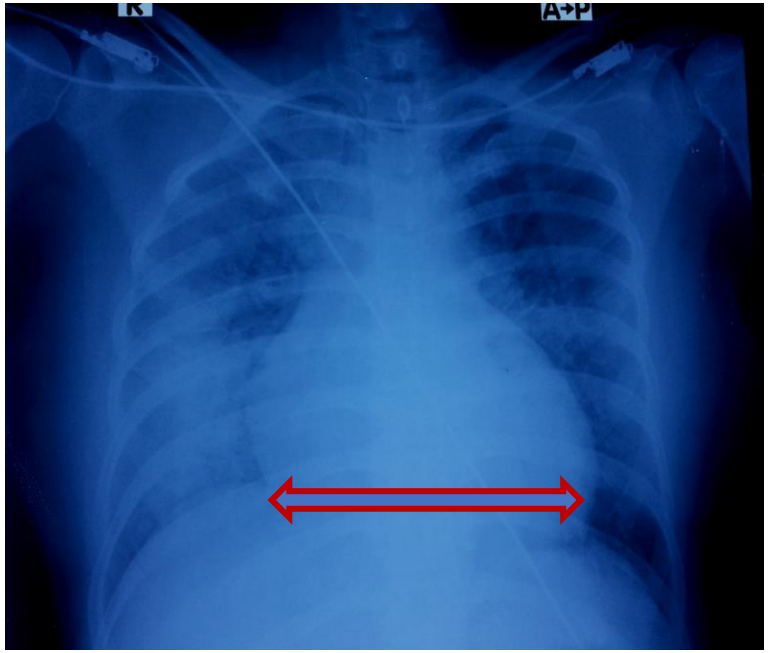


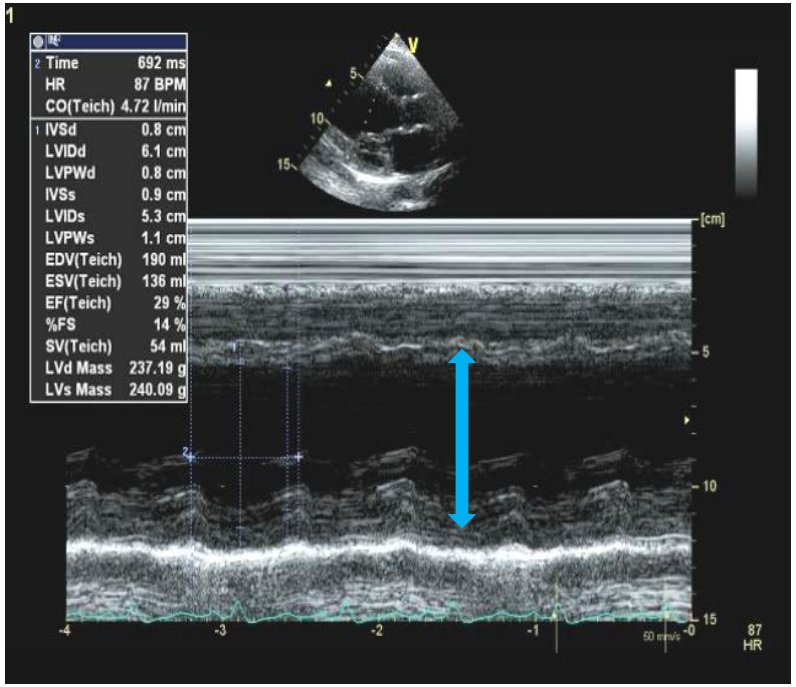
Ref : 2021 ESC guidelines for diagnosis and treatment of acute and chronic heart failure

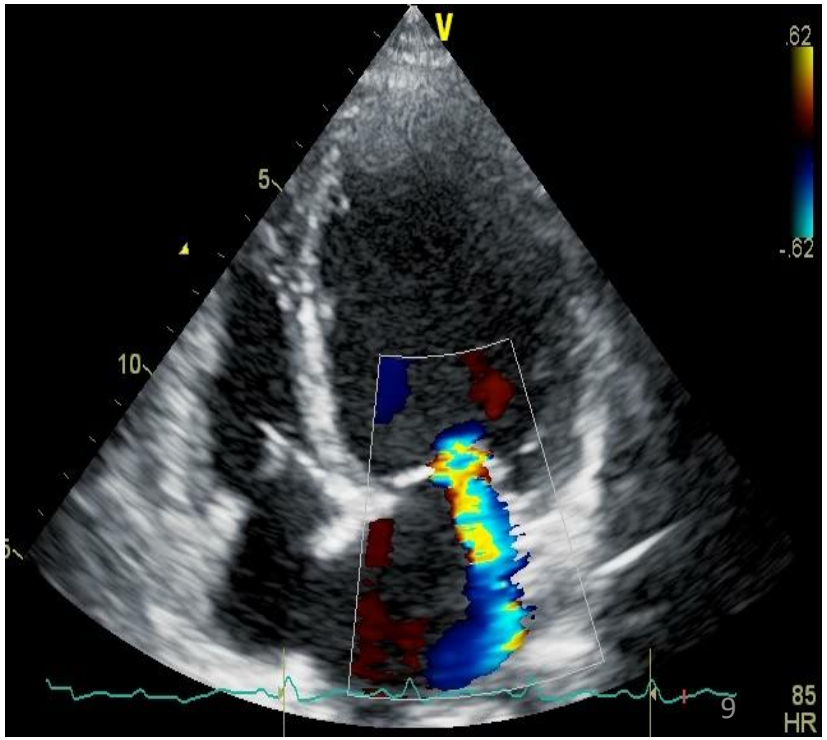
Proposed algorithm for diagnosis of heart failure



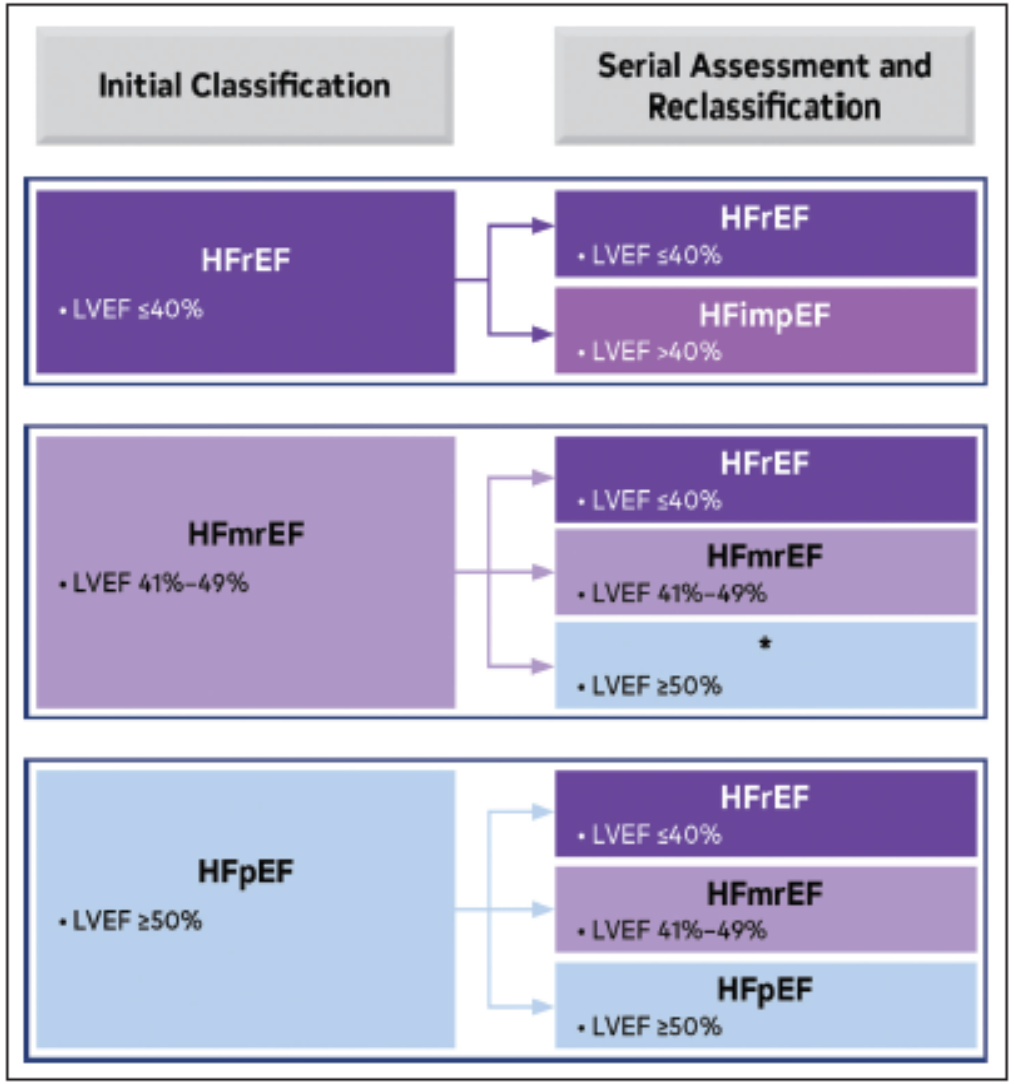
Ref : Asian Pacific Society of Cardiology Consensus Statements on the Diagnosis and Management of Chronic Heart Failure , Journal of Asian Pacific Society of Cardiology, 2023


R
A→P


Time 692 ms
HR 87 BPM
CO(Teich) 4.72 l/min
IVSd 0.8 cm
LVIDd 6.1 cm
LVPWd 0.8 cm
IVSs 0.9 cm
LVIDs 5.3 cm
LVPWs 1.1 cm
EDV(Teich) 190 ml
ESV(Teich) 136 ml
EF(Teich) 29 %
%FS 14 %
SV(Teich) 54 ml
LVd Mass 237.19 g
LVs Mass 240.09 g
[cm]
87
HR

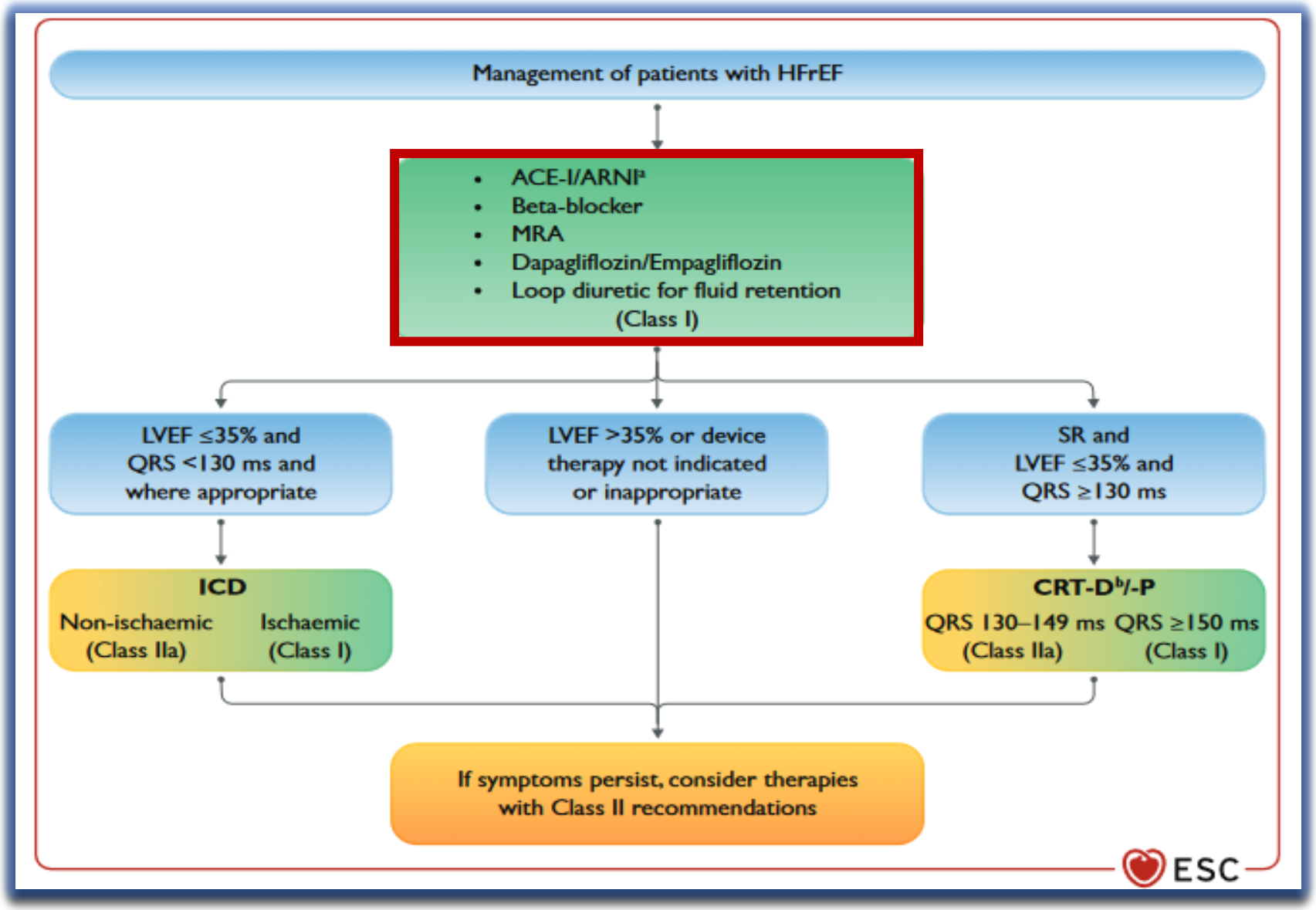

.62
-.62
85
HR

Classification and Trajectories of HF Based on LVEF



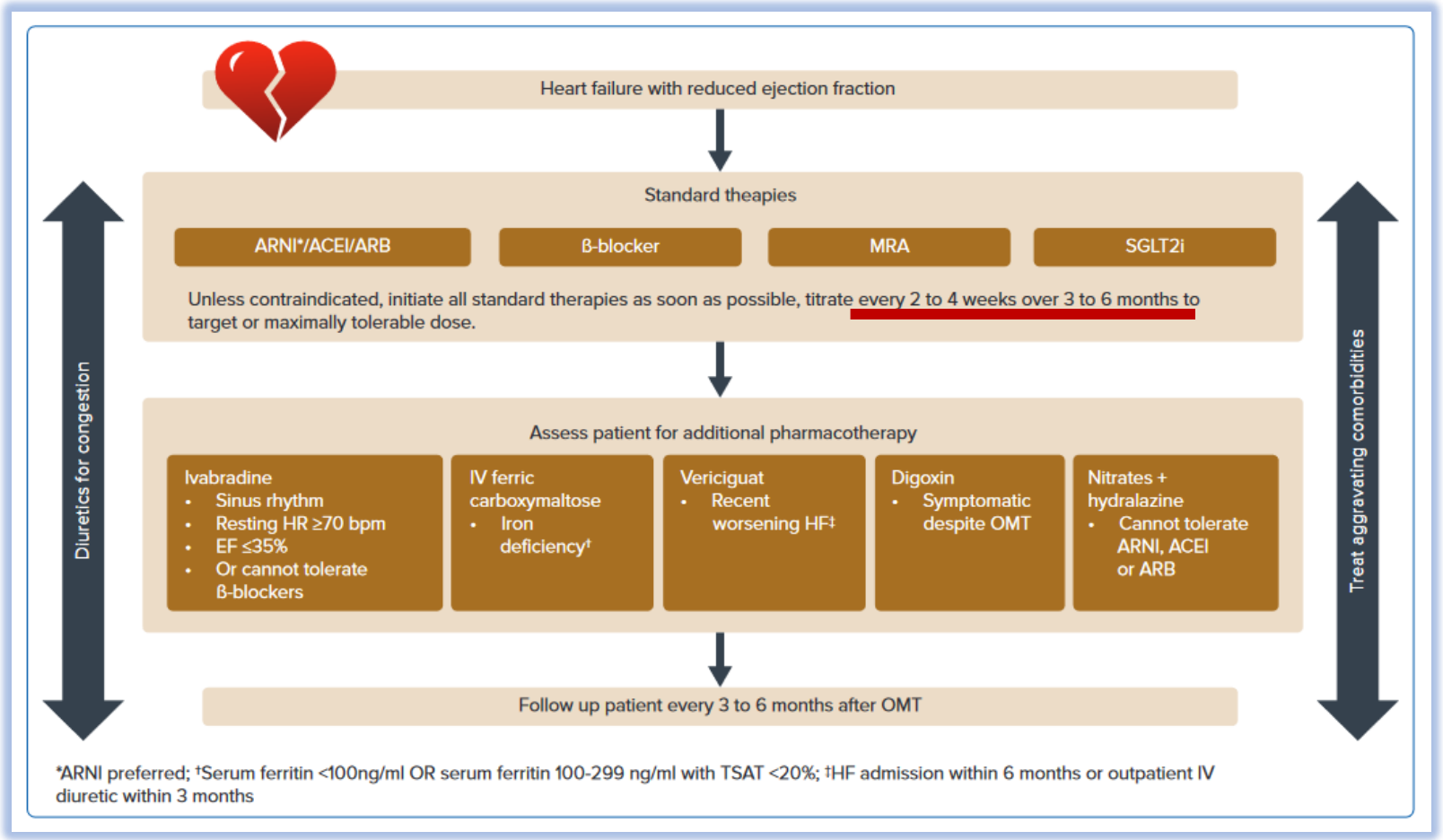
Heart Failure with reduced ejection fraction (HFrEF)

Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction



Ref : 2021 ESC guidelines for diagnosis and treatment of acute and chronic heart failure

Proposed algorithm for the pharmacotherapy of heart failure with reduced ejection fraction



Ref : Asian Pacific Society of Cardiology Consensus Statements on the Diagnosis and Management of Chronic Heart Failure , Journal of Asian Pacific Society of Cardiology, 2023

Site of action of drugs used in treatment of heart failure

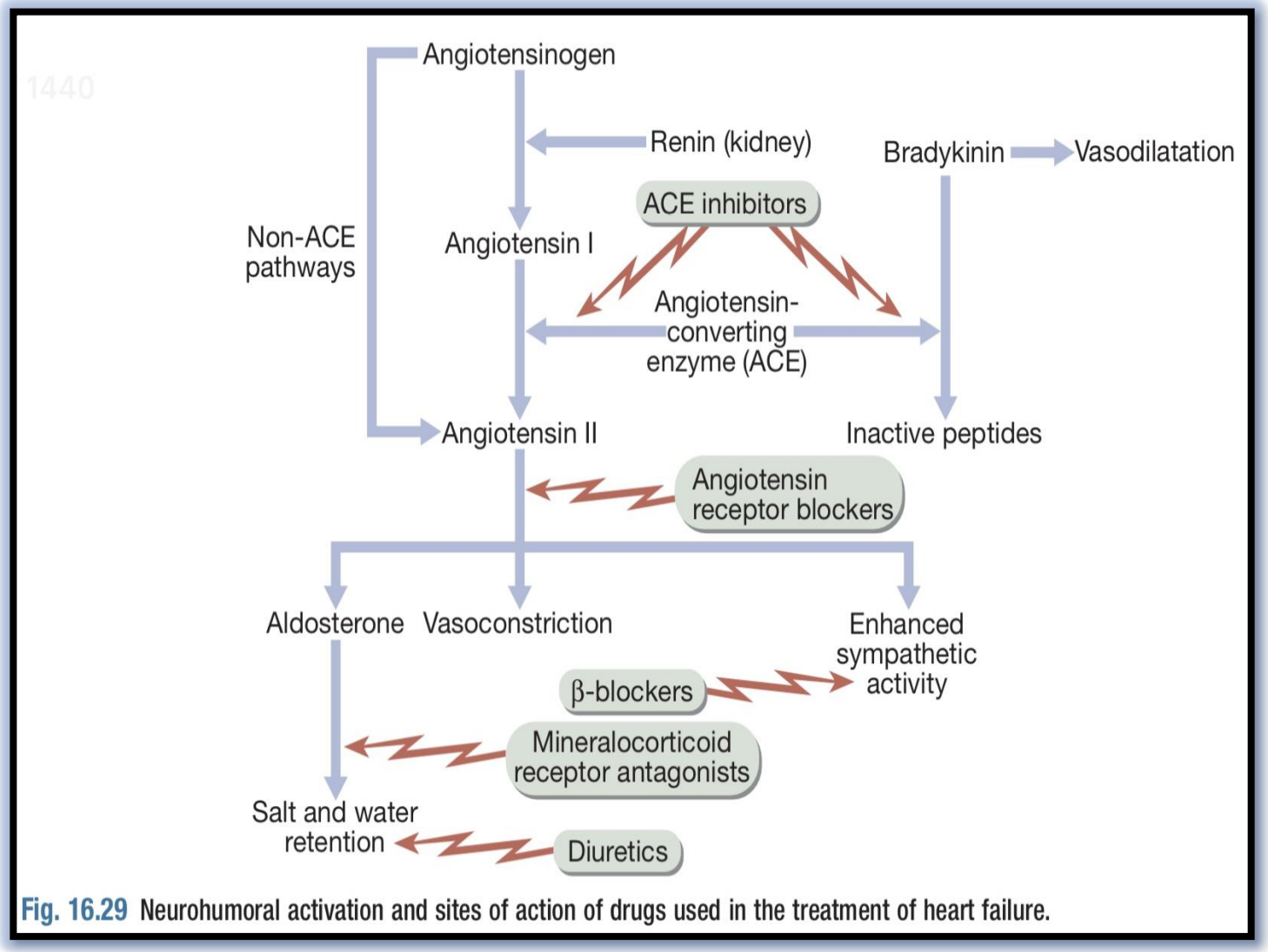
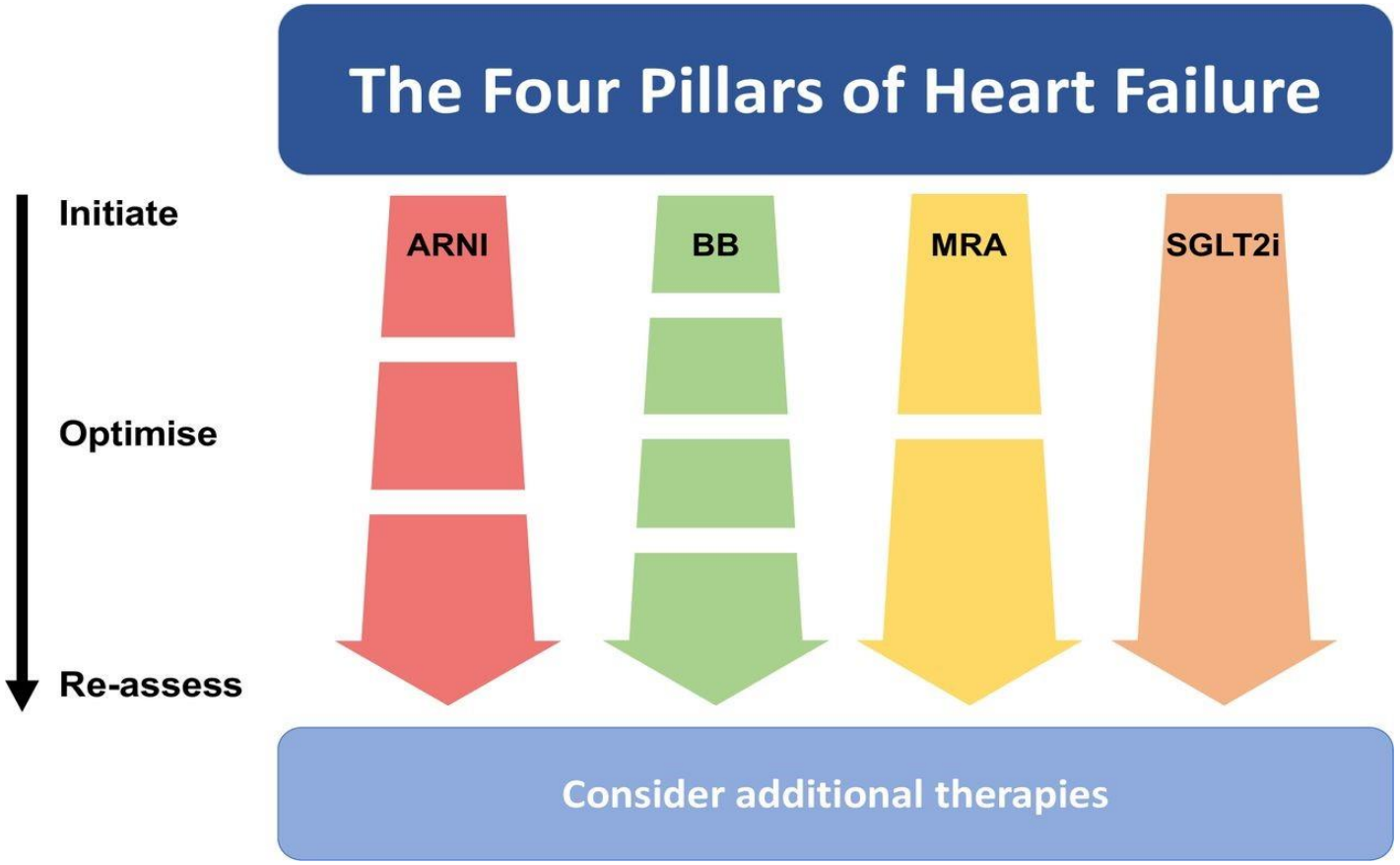


Fig. 16.29 Neurohumoral activation and sites of action of drugs used in the treatment of heart failure.

Four pillars of heart failure : contemporary pharmacological therapy for HFrEF



Points to note …

- If patients cannot tolerate ARNIs or ACEIs, ARBs may be used instead
- Only a few ARBs (candesartan, losartan and valsartan) are supported by RCTs and **no ARB has yet been shown to reduce all-cause mortality**
- The maximally tolerated dose may be slightly **lower in Asian** people compared with Western patients due to differences in body size
- **Up titration of an individual medication should not be done at the expense of the addition of one of the other four foundational medications**.

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.*

Pre-discharge and early post discharge phase

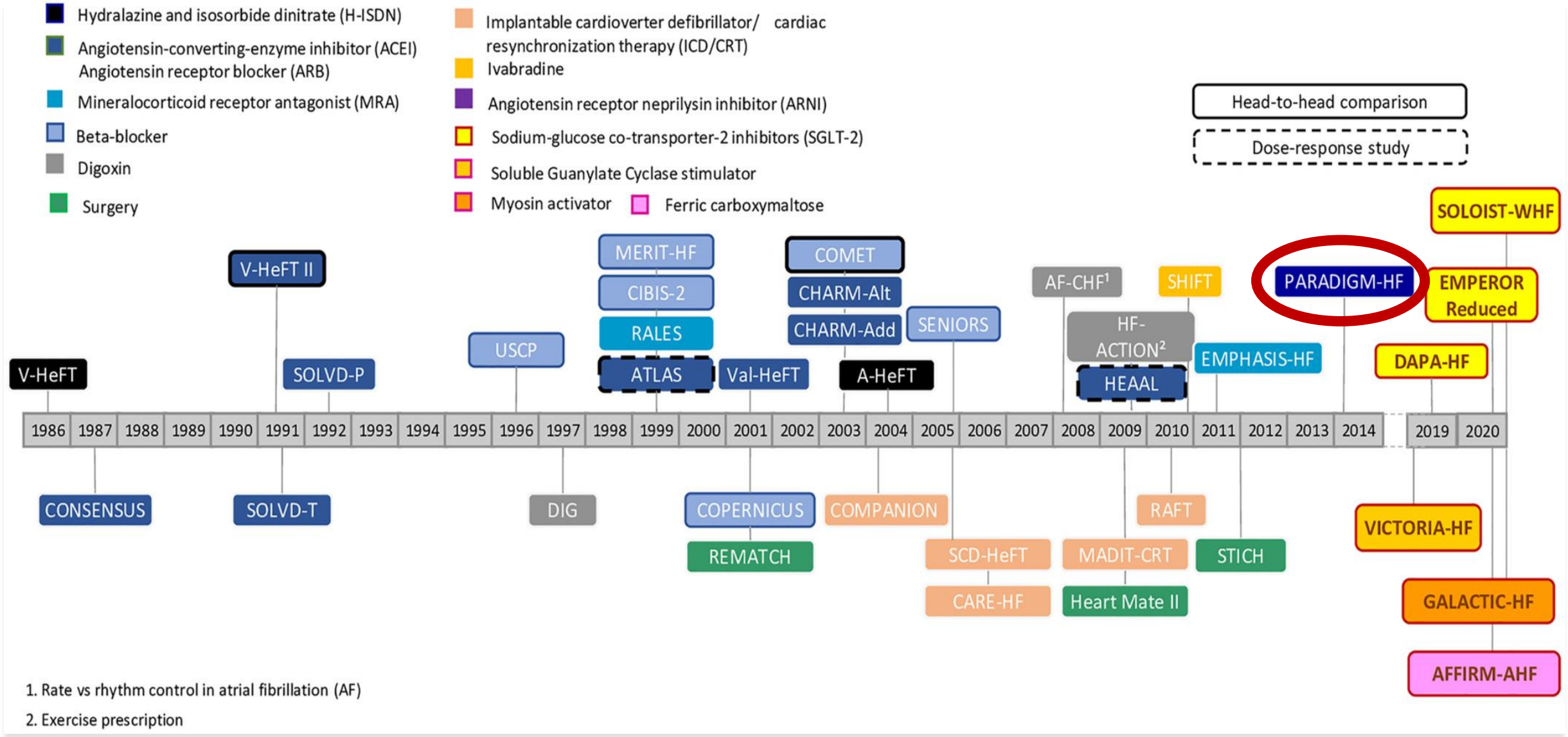
- The goal of first titration visit – ***within 48 hours*** before discharge – to reach ***at least half of the dose*** of recommended medications.

- Titration to ***full target doses*** of oral therapies – attempted ***within 2 weeks*** after discharge – with appropriate safety and monitoring

- ***High intensity care*** for initiation and rapid up-titration of oral HF therapies and close follow up ***in first 6 weeks after discharge*** for acute heart failure hospitalization –recommended to reduce heart failure hospitalization and all cause death ***(STRONG-HF trial).***

What about evidence ?

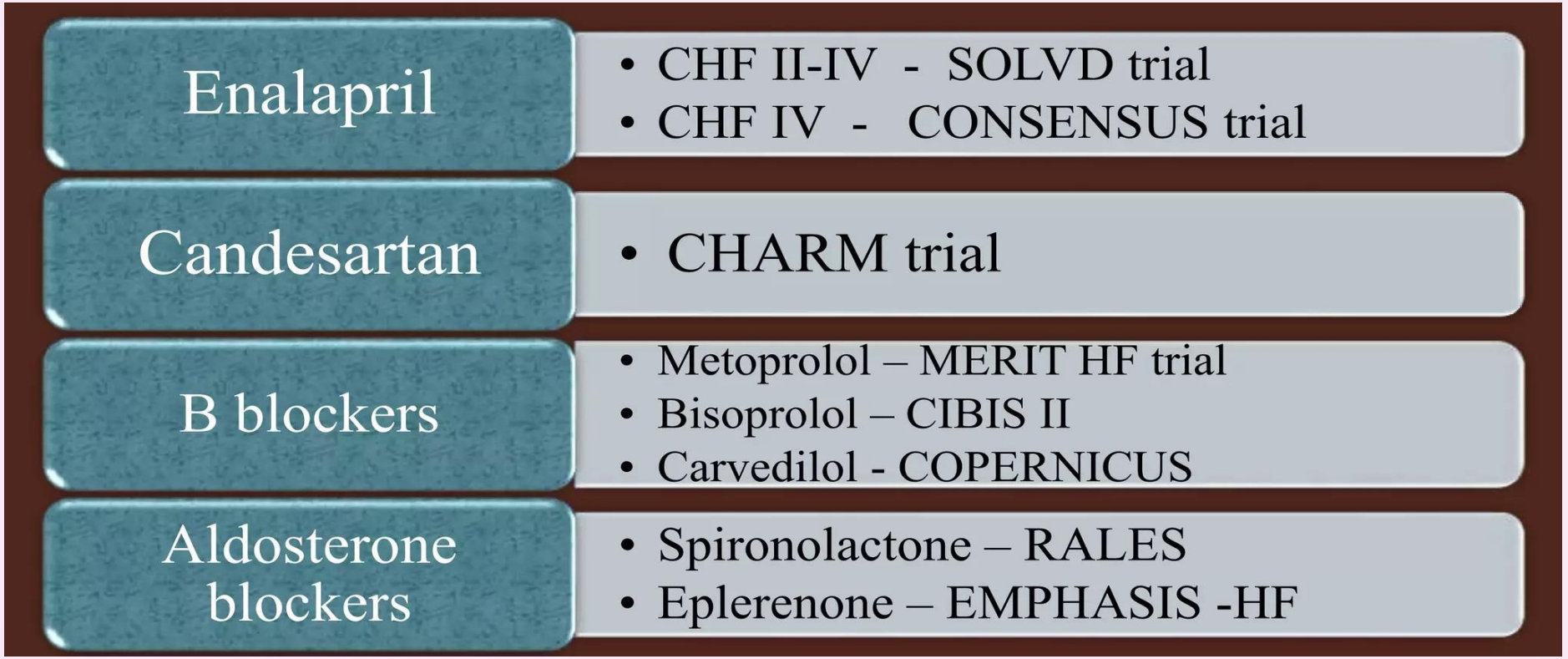
Heart failure in the last year: progress and perspective



1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

ESC Heart Failure, Volume: 7, Issue: 6, Pages: 3505-3530, First published: 05 December 2020, DOI: (10.1002/ehf2.13124)

Trial evidence of mortality benefit of drugs in heart failure



PARADIGM-HF

(**P**rospective Comparison of **A**ngiotensin **R**eceptor–**N**eprilysin **I**nhibitor With **A**ngiotensin-Converting Enzyme Inhibitor to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure)

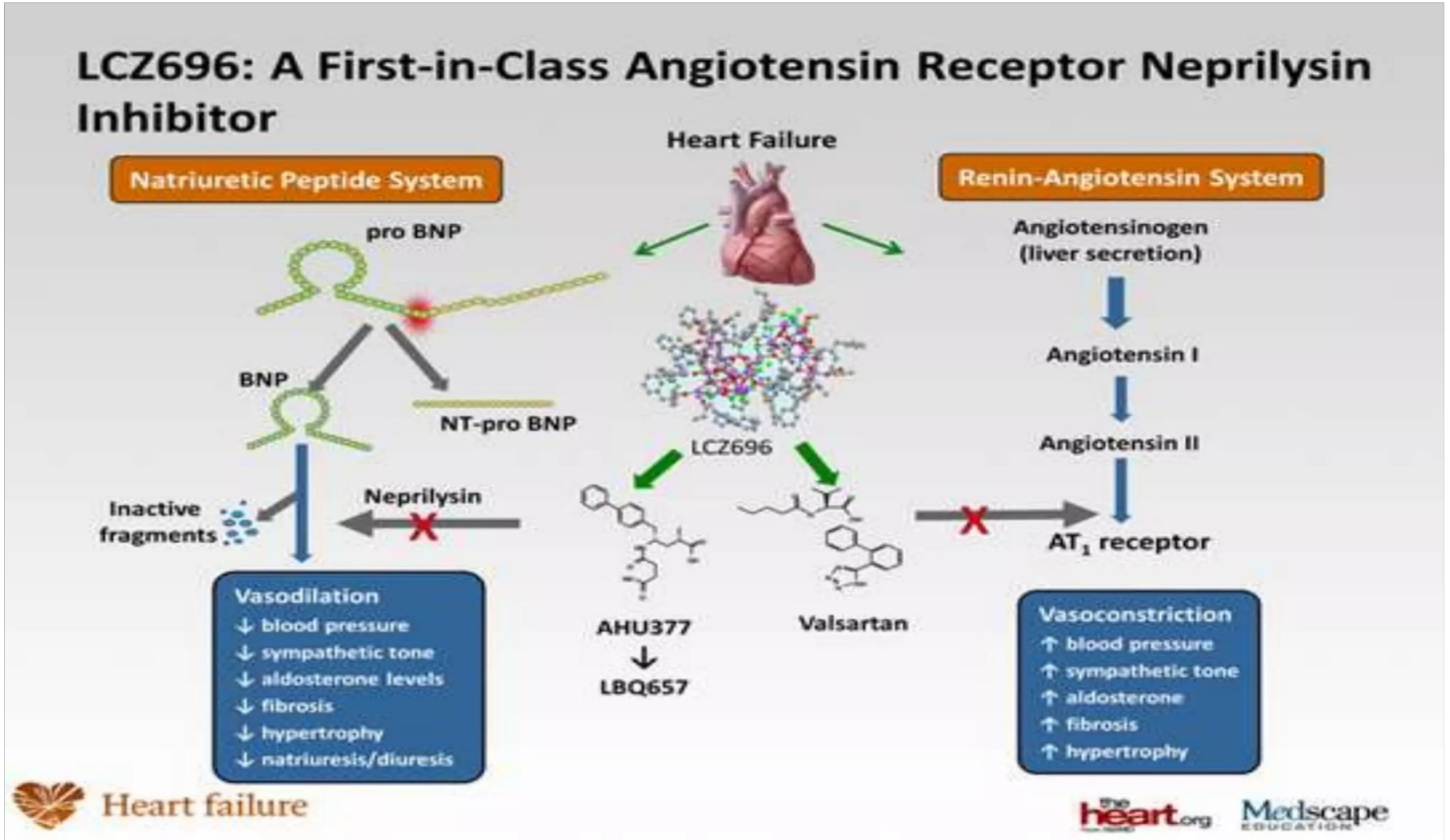
Angiotensin Receptor – Neprilysin inhibitor (ARNI)

Vs

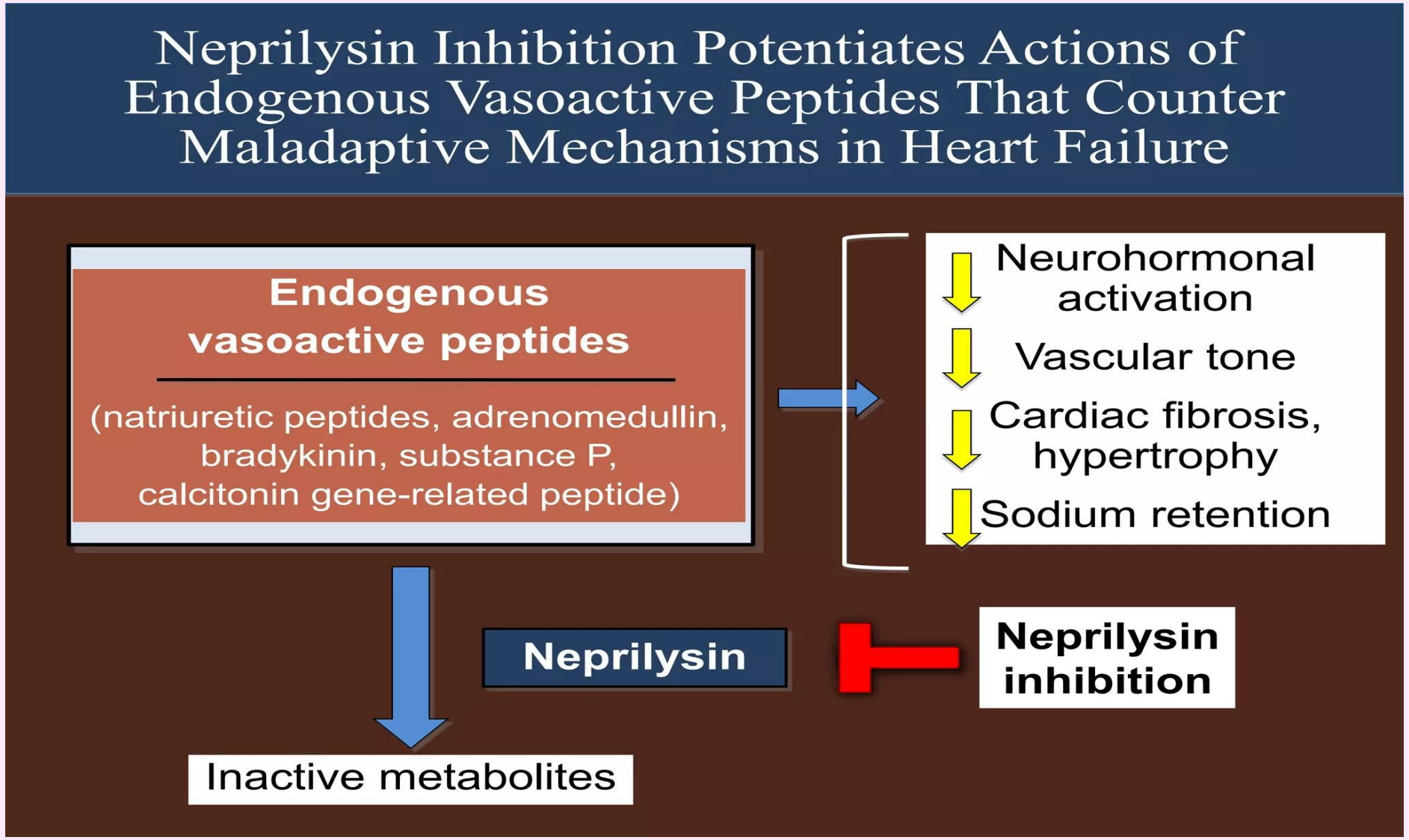
Angiotensin converting enzyme inhibitor Enalapril

in heart failure

Mechanism of action of ARNI



Benefit of Neprilysin inhibition

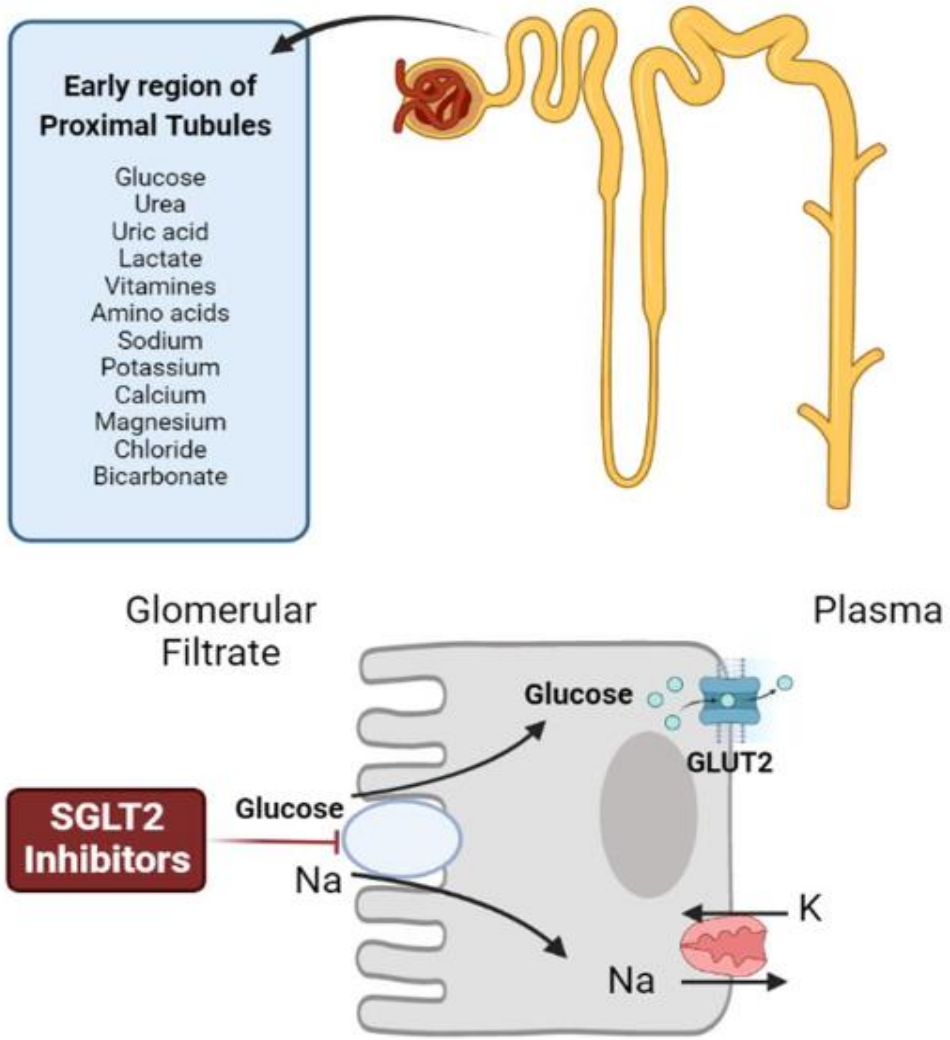


PARADIGM-HF Key results

- 20 % reduction in primary endpoint (CV death or HF hospitalization)
- 20 % reduction in CV death
- 21 % reduction in heart failure hospitalization
- 16 % reduction in all cause mortality

Sodium Glucose co-transporter 2 (SGLT 2) inhibitors

Mechanism of action of SGLT 2 inhibitors



Cardiovascular benefits of SGLT 2 inhibitors in heart failure

- ***Multi dimensional CV benefits*** in HF

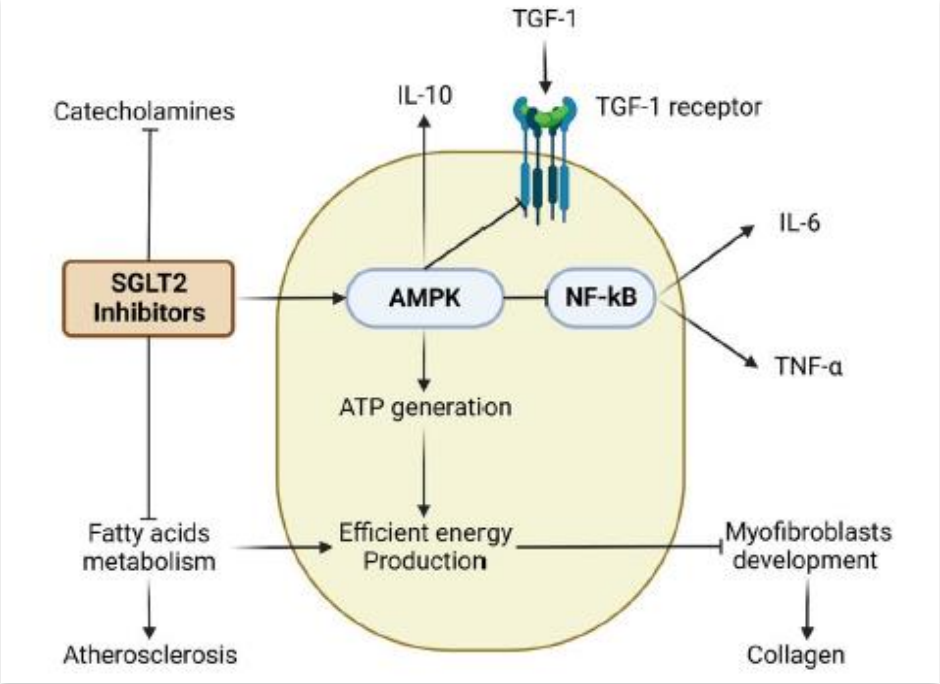
  - Mild diuretic effect
  - Decrease sodium → sodium homeostasis → decrease plasma volume and BP → decrease afterload
  - Reduced circulating volume → reduced preload
  - Its inhibition promotes diuresis and reduces preload, after- load, and blood pressure
  - Smooth muscle relaxation → improve arterial stiffness
  - Protective effect on cardiac myocytes

How does SGLT 2 inhibitors work:
? The broad cardiorenal effects of SGLT2 inhibitors

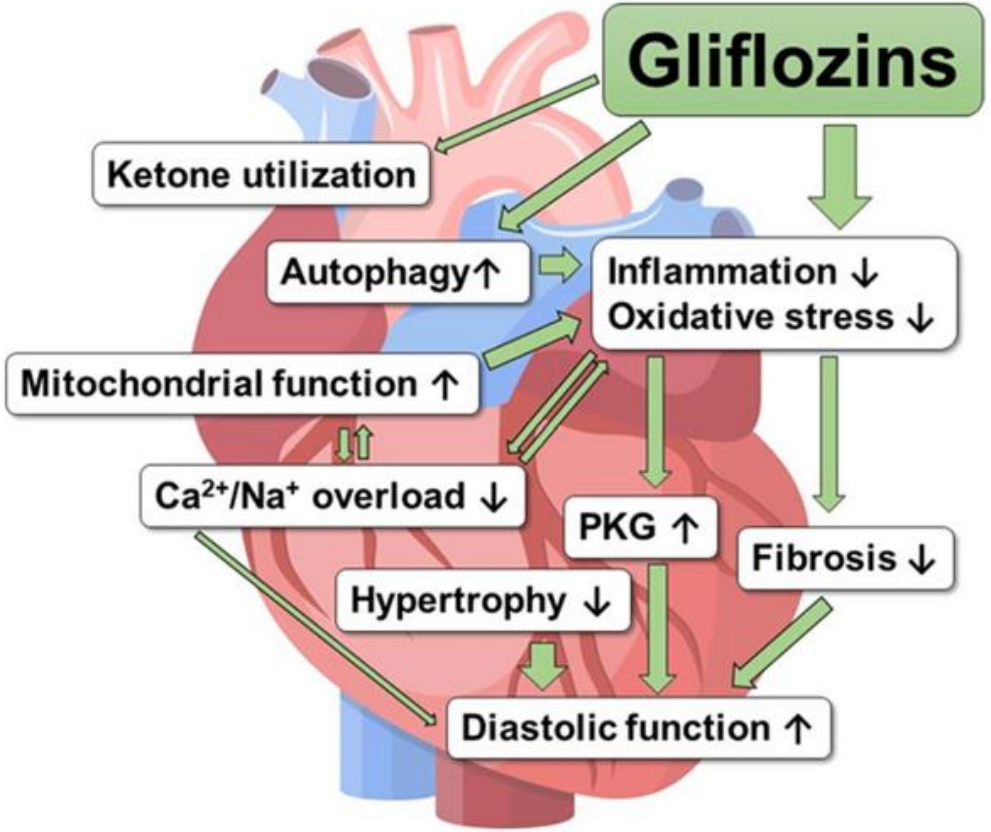
- Directly **increase renal erythropoietin** and the oxygen carrying capacity of the blood
- Constant glycosuria by itself has a direct cardiac benefit by shifting metabolism in favor of **oxidation of free fatty acids**, which in turn optimizes **mitochondrial function in cardiac myocytes** (improving contractile function)
- **Reduces epicardial fat** (decreasing noxious inflammation and fibrosis associated with heart failure)
- These mechanisms may explain the **reduction in left ventricular mass index**, a known predictor of major adverse cardiovascular events, seen on cardiac magnetic resonance imaging and associated with empagliflozin and dapagliflozin use

Other Cardiovascular benefits of SGLT 2 inhibitors

	Dapagliflozin	Empagliflozin	Canagliflozin
Cardiovascular effects	Decreased collagen formation Activated IL 10	Inhibited fibroblast activation Reduced sympathetic overdrive Reduced atherosclerosis Decrease renal production of inflammatory cytokines	Decreased TNF R1 and proinflammatory cytokines Inhibited intracellular glucose metabolism Promoted autophagy



Proposed myocardial mechanisms of Gliflozins



What about the evidence for SGLT 2 inhibitors ?

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced)

EMPEROR-Reduced

Inclusion Criteria

The study included patients with **chronic HF** with reduced ejection fraction

Key inclusion criteria:

- NYHA class II–IV with **LVEF ≤40%**
- Elevated NT-proBNP
- Guideline-recommended medication stable ≥1 week prior to first visit
- eGFR **≥20** ml/min/1.73 m^2

	Elevated NT-proBNP	
EF (%)	NT-proBNP (pg/ml) Patients without AF*	NT-proBNP (pg/ml) Patients with AF*
≥36 to ≤40	≥2500	≥5000
≥31 to ≤35	≥1000	≥2000
≤30	≥600	≥1200
≤40% + HHF within 12 months	≥600	≥1200

EMPEROR-Reduced Trial Specified Only Three Endpoints to be Tested in Hierarchical Manner

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

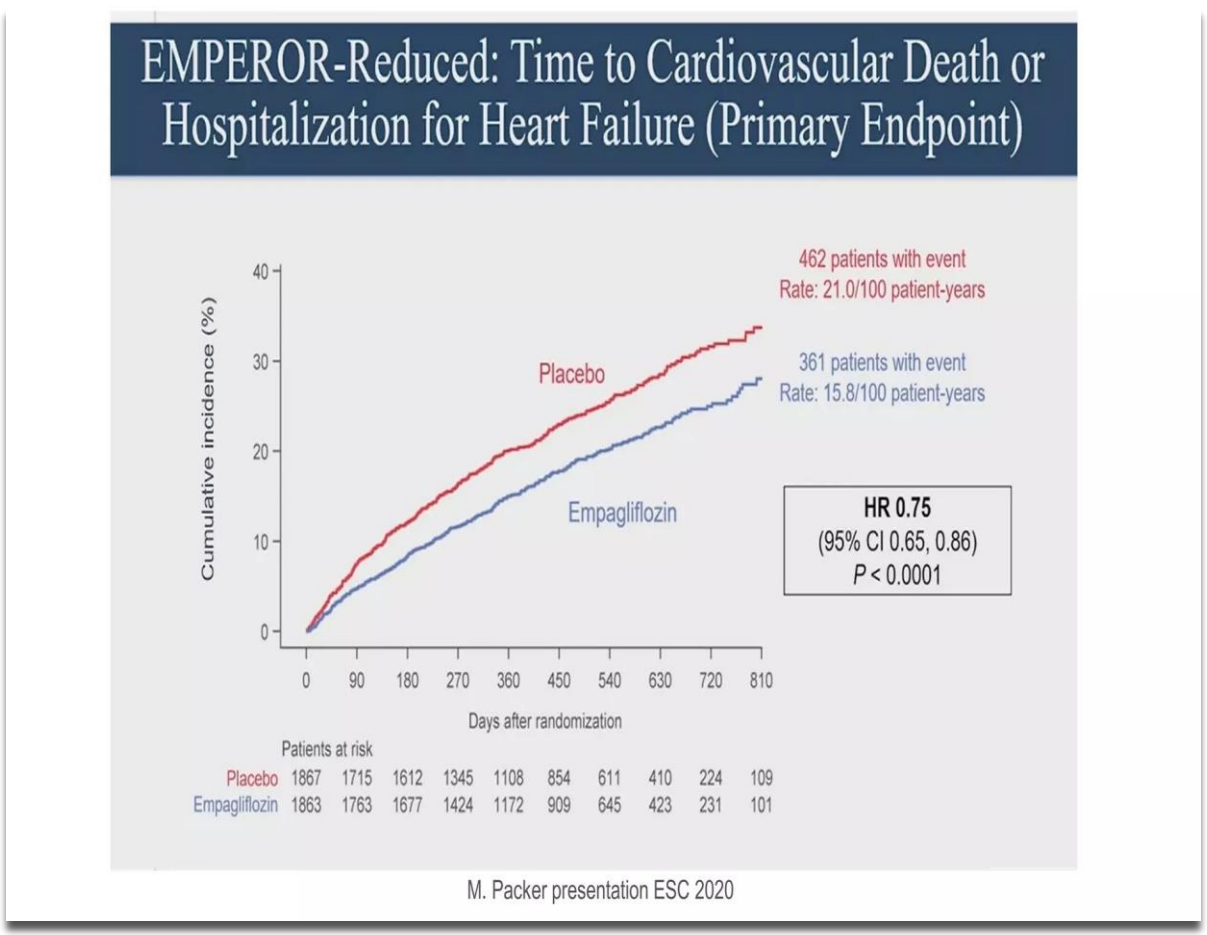
First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)

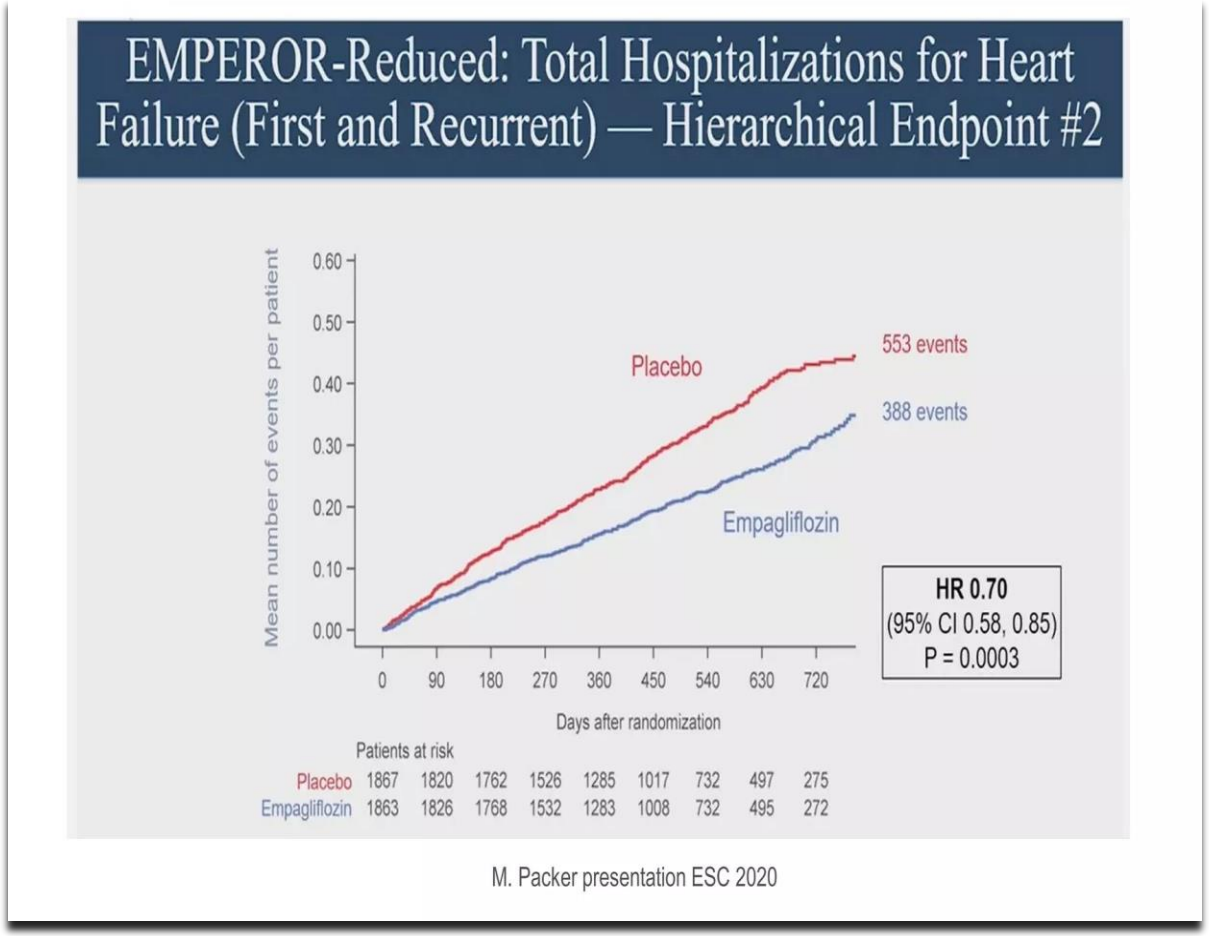
Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

Other prespecified endpoints: Composite renal endpoint, KCCQ clinical summary score, total number of hospitalizations for any reason, all-cause mortality, new onset diabetes

M. Packer presentation ESC 2020

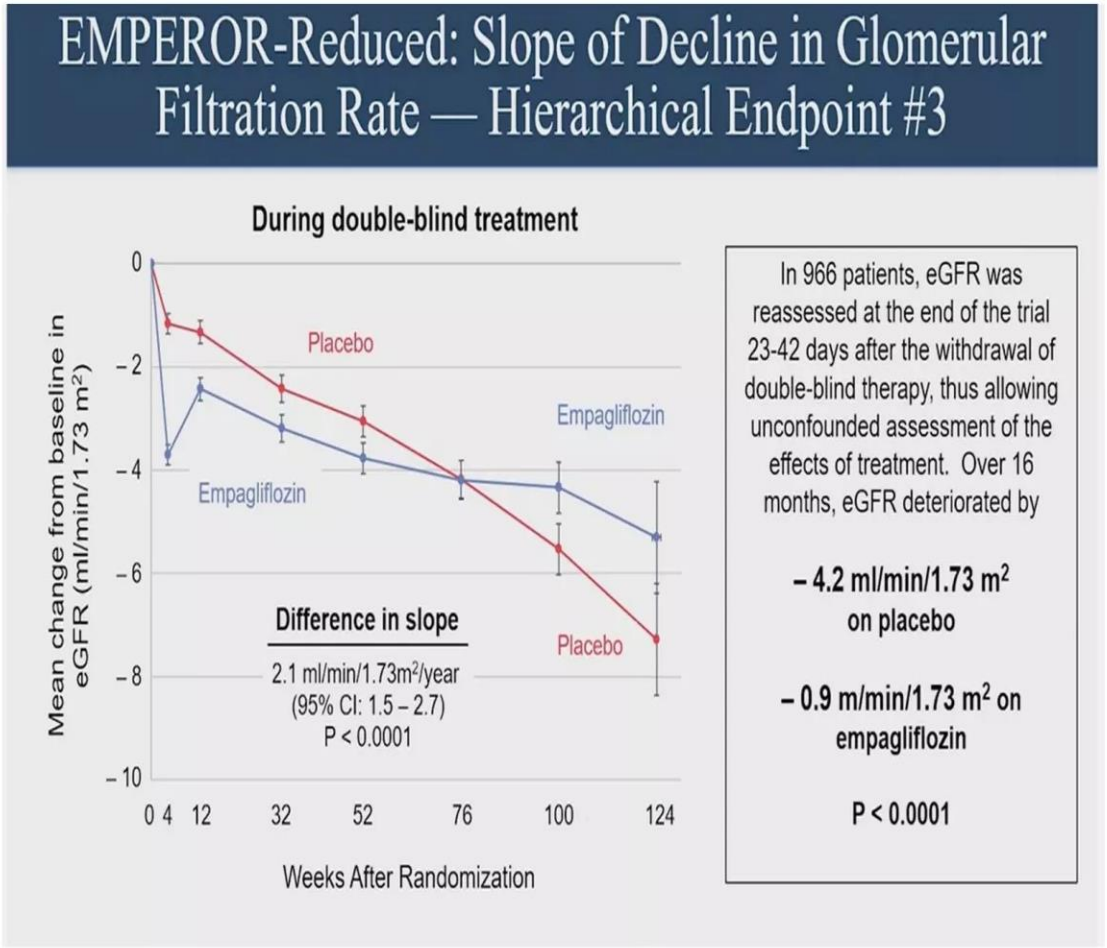
EMPEROR-Reduced



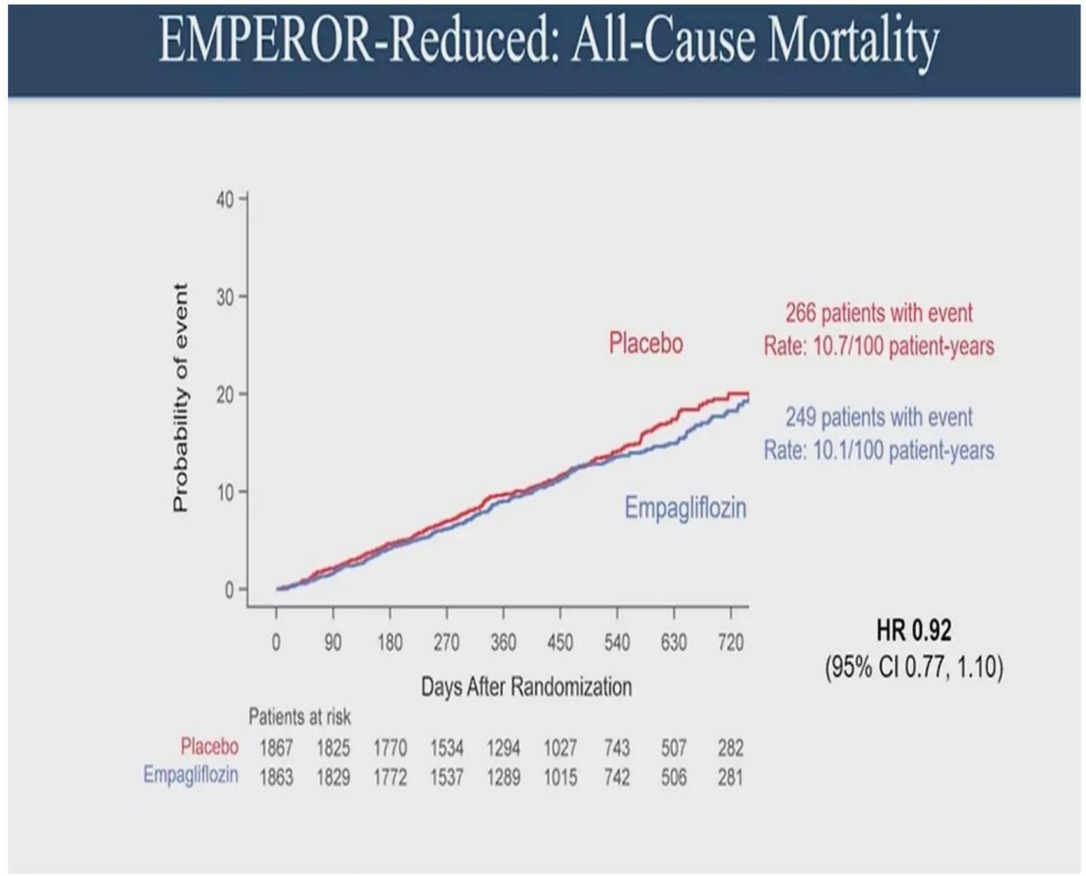


25% reduction in the combined risk of the primary outcomes of CV death and hospitalization for HF regardless of T2D status

EMPEROR-Reduced



M. Packer presentation ESC 2020



M. Packer presentation ESC 2020

EMPEROR-Reduced : Adverse Events

EMPEROR-Reduced: Adverse Events

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of special interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

M. Packer presentation ESC 2020

Adverse reactions of SGLT2 inhibitors

- Most frequent - genital mycotic infection, such as **vulvovaginal candidiasis** (4-5 times more common in women).
- Rare but serious - serious **urinary tract infections** such as **pyelonephritis** and **urosepsis** and necrotizing fasciitis of the perineum (Fournier's gangrene).
- Risk of intravascular volume contraction and **hypotension**, especially in older adults and patients taking other diuretic medications.
- Canagliflozin is associated with an increased risk of lower limb amputations.
- SGLT2 inhibitors are **contraindicated in type 1 diabetes mellitus** because they promote ketone production and may increase the risk of diabetic ketoacidosis

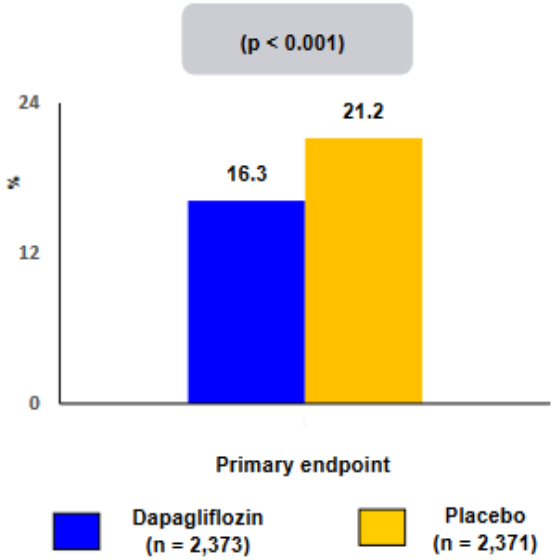
Dapagliflozin in HFrEF

DAPA-HF

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with heart failure with reduced ejection fraction (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily vs. placebo.



RESULTS

- Primary efficacy endpoint: cardiovascular death, hospitalization for heart failure, or urgent heart failure visit occurred in 16.3% of the dapagliflozin group compared with 21.2% of the placebo group (p < 0.001)
- Cardiovascular death: 9.6% with dapagliflozin vs. 11.5% with placebo
- Hospitalization for heart failure: 9.7% with dapagliflozin vs. 13.4% with placebo

CONCLUSIONS

- Among patients with symptomatic heart failure due to reduced left ventricular ejection fraction, dapagliflozin was beneficial
- Dapagliflozin vs. placebo was associated with a reduction in cardiovascular deaths and heart failure events

McMurray JJ, et al. N Engl J Med 2019;Sep 19:[Epub]

Vericiguat (Oral soluble guanylyl cyclase stimulator)

- Directly binds and stimulates sGC and increases cGMP production.
- cGMP has several potentially beneficial effects in patients with HF, including
  - Vasodilation
  - Improvement in endothelial function
  - Decrease in fibrosis and remodeling of the heart

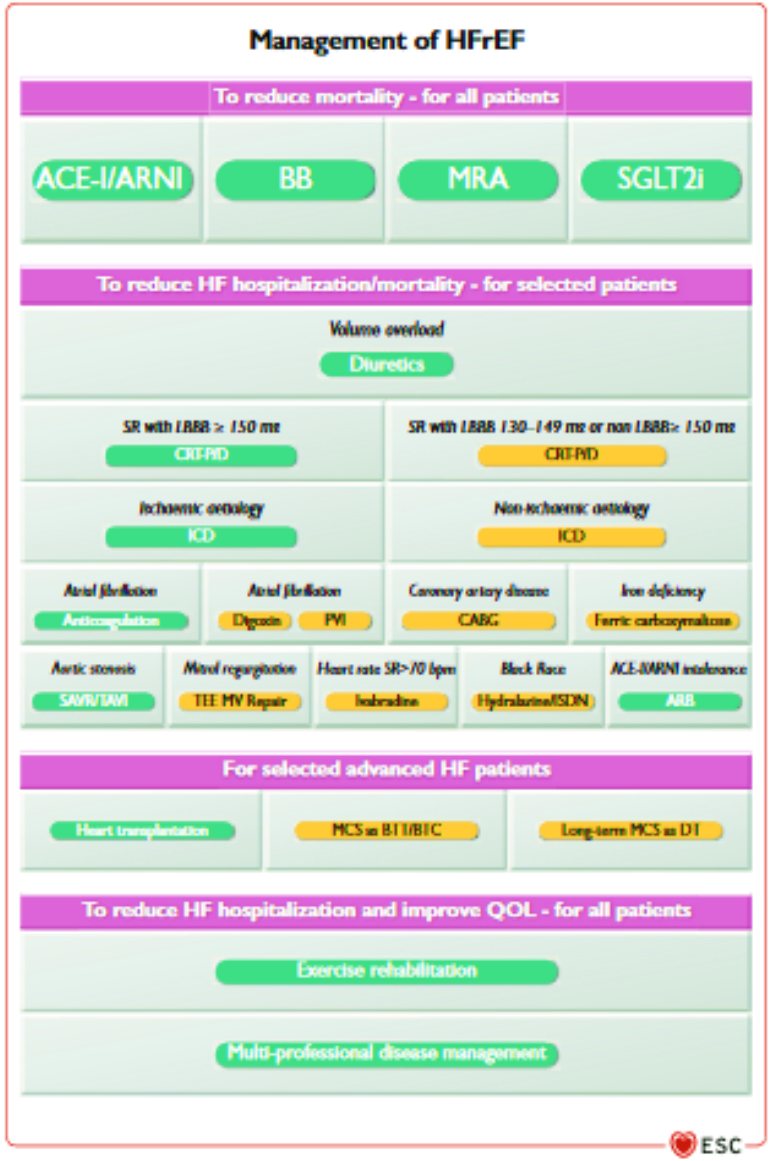
VICTORIA trial

- Relative risk reduction of **10 %** in the primary outcome (cardiovascular death of HF hospitalization) was lower than expected

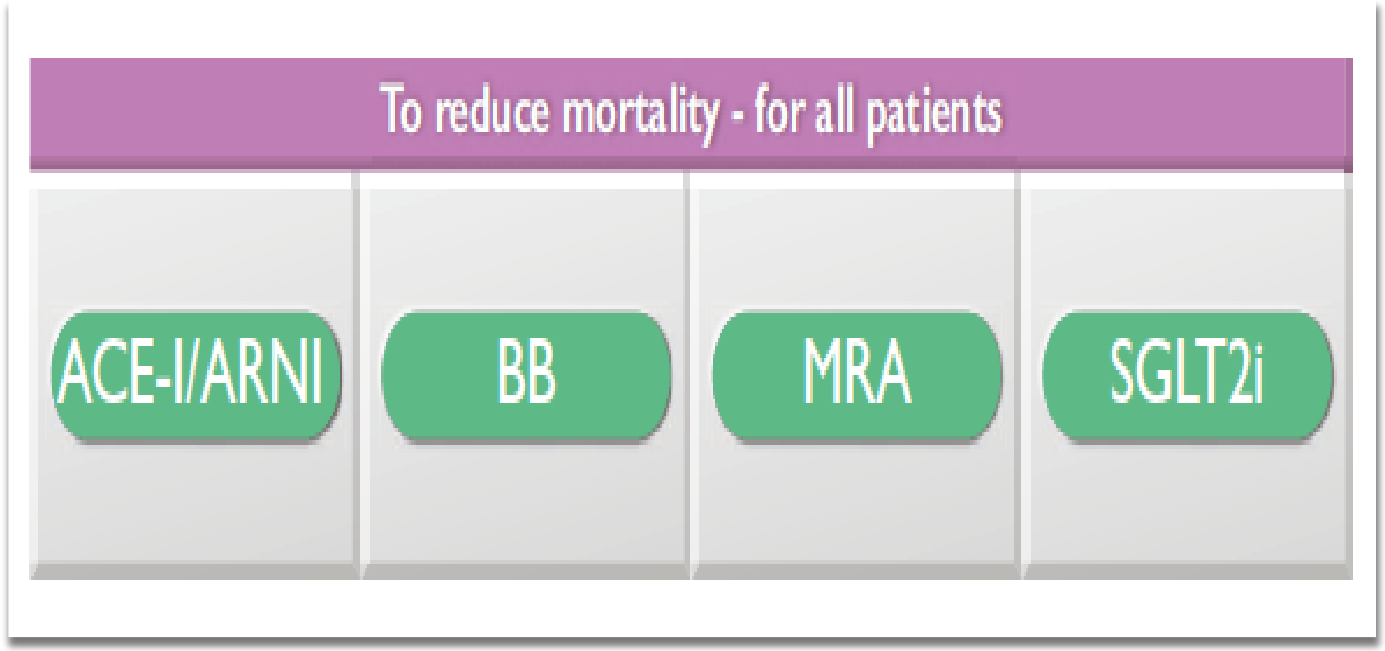
Recommendation for Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.[1]

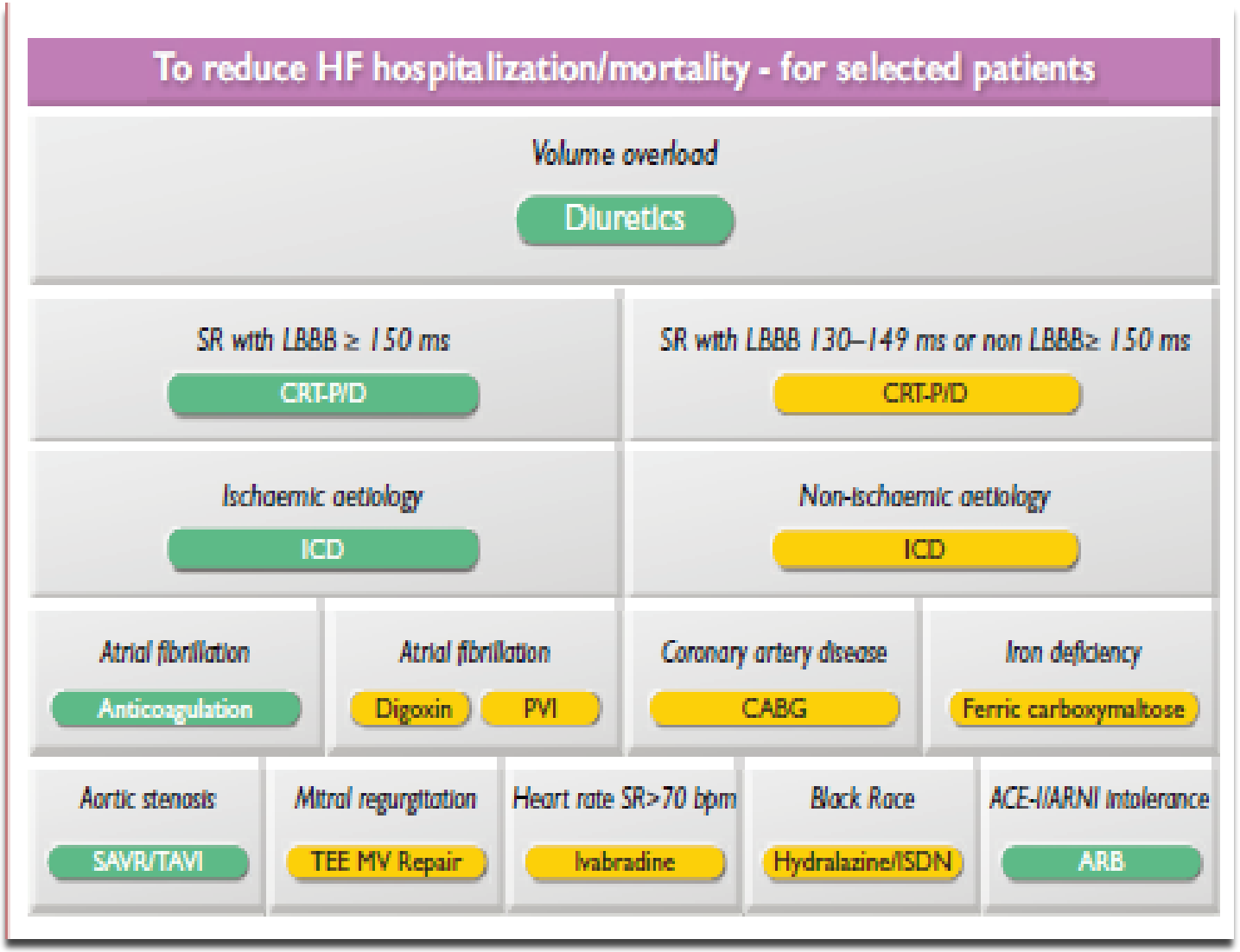
Strategic phenotypic overview of the management of heart failure with reduced ejection fraction



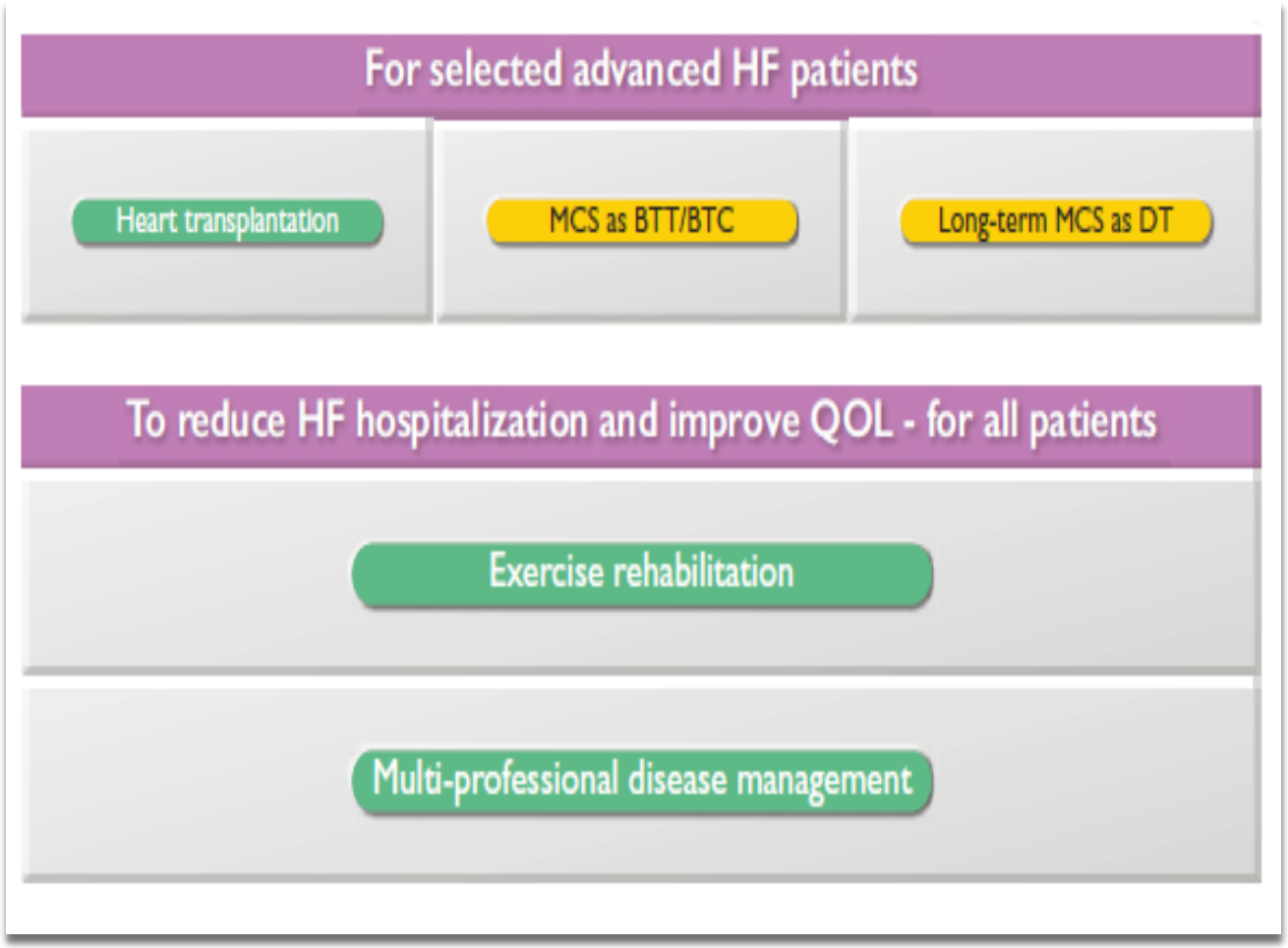
Management of HFrEF



Management of HFrEF



Management of HFrEF

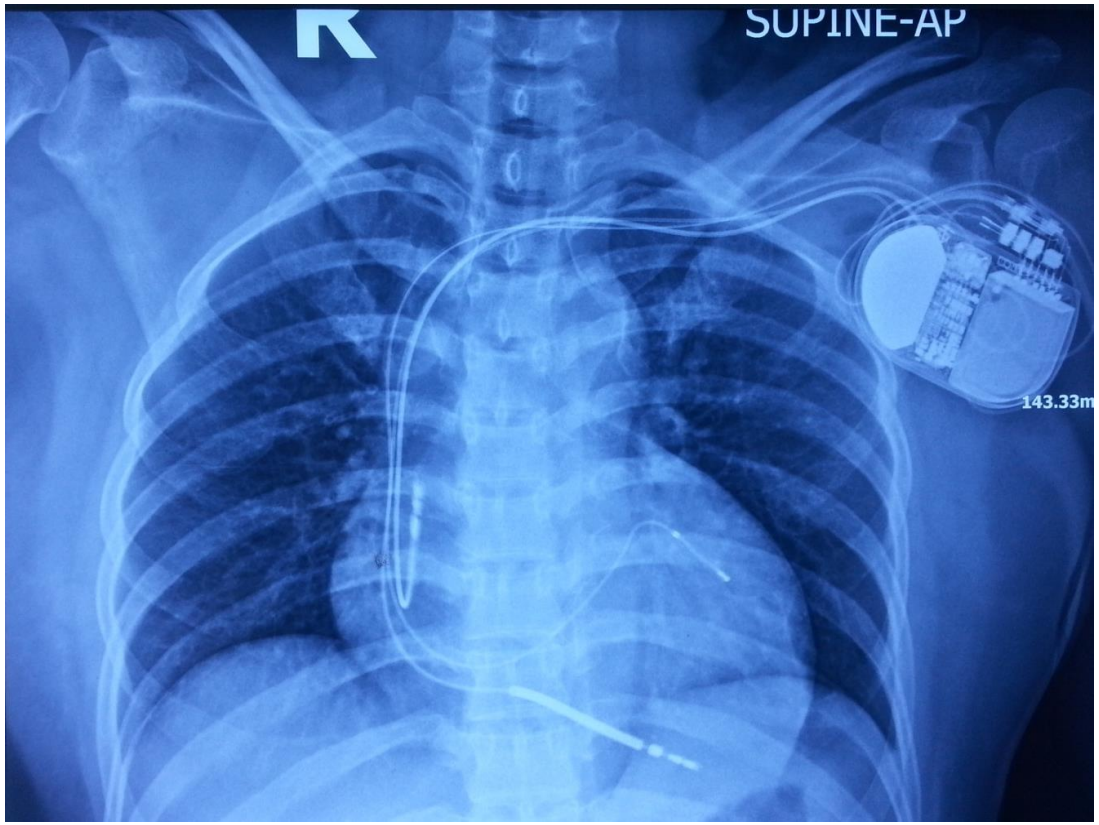


Cardiac implantable electronic devices (CIED) therapy

- Patients with LVEF ≤35% after 3 months of achieving OMT should be referred for cardiac implantable electronic devices therapy.

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

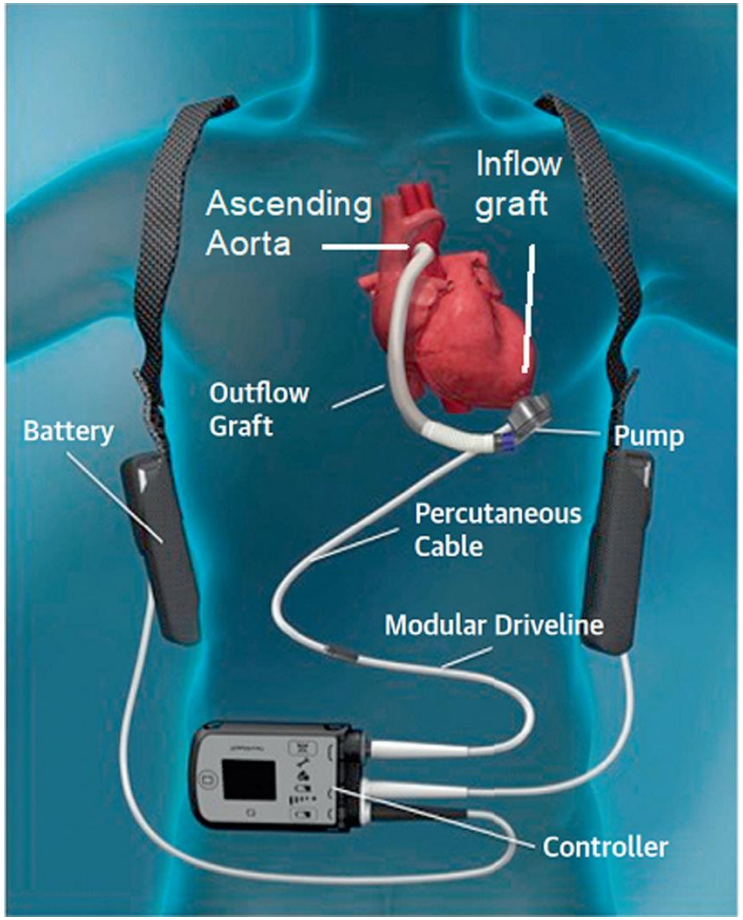
Recommendations	Class[a]	Level[b]
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	I	A
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.[216–219]	I	A



Timely referral to Cardiology

- Advanced intervention for heart failure including **LVADs** or **heart transplantation**
- Patients with advanced HF, NYHA class III or IV, and/or an EF of less than 25% should be referred to a cardiologist at an advanced HF center.
- Other indications for referral to cardiology include
  - patients with HF who exhibit early organ dysfunction
  - persistent hypotension (systolic BP < 90 to 100 mm Hg)
  - maximally tolerated GDMT
  - at least one hospitalization for HF within the past 12 months
  - continuing edema despite increased diuretic use
  - history of ventricular arrhythmias resulting in hemodynamic instability

Left ventricular assist device



Mechanical circulatory device (MCS)

- Bridge to Transplantation (BTT)
- Bridge to Candidacy(BTC)
- Long term MCS as Destination therapy (DT)

Heart Failure with preserved LVEF (HFpEF)

HFpEF diagnostic scoring system
H_2FPEF

H_2	**H**eavy (BMI >30 kg/m^2)	2
	On ≥2 anti**H**ypertensives	1
F	Atrial **F**ibrilllation	3
P	**P**ulmonary hypertension (PASP >35 mm Hg on Doppler echocardiography	1
E	**E**lder (age >60 years)	1
F	**F**illing pressure (E/e' >9 on Doppler echocardiography)	1

≥6 points: highly diagnostic of HFpEF

Ref : 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction

HFpEF diagnostic scoring system

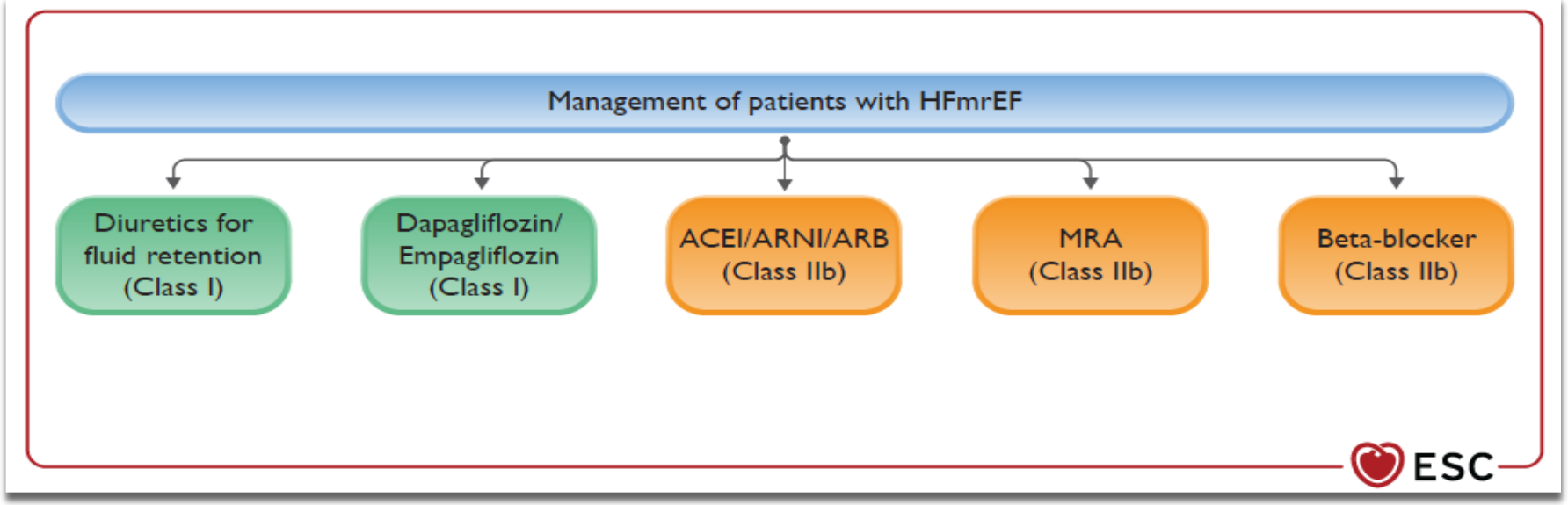
Symptoms and signs of HF

An LVEF ≥ 50%

Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/ raised LV filling pressures, including raised NPs

Parameter[a]	Threshold
LV mass index Relative wall thickness	≥95 g/m^2 (Female), ≥115 g/m^2 (Male) >0.42
LA volume index[a]	>34 mL/m^2 (SR)
E/e' ratio at rest[a]	>9
NT-proBNP BNP	>125 (SR) or >365 (AF) pg/mL >35 (SR) or >105 (AF) pg/mL
PA systolic pressure TR velocity at rest[a]	>35 mmHg >2.8 m/s

Management of HFmrEF

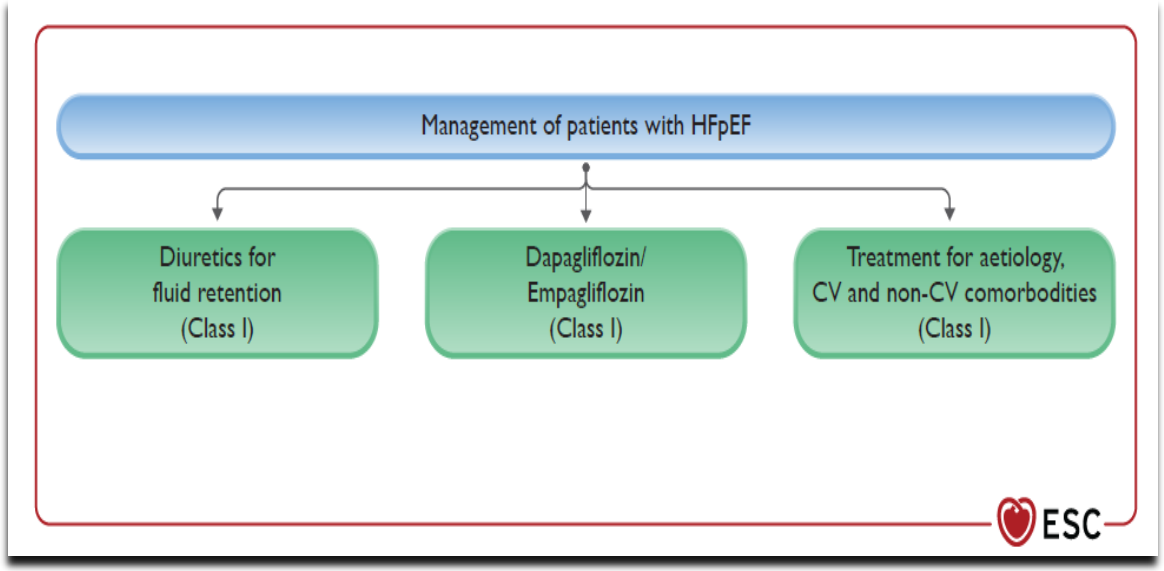


Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Ref : 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Management of HFpEF

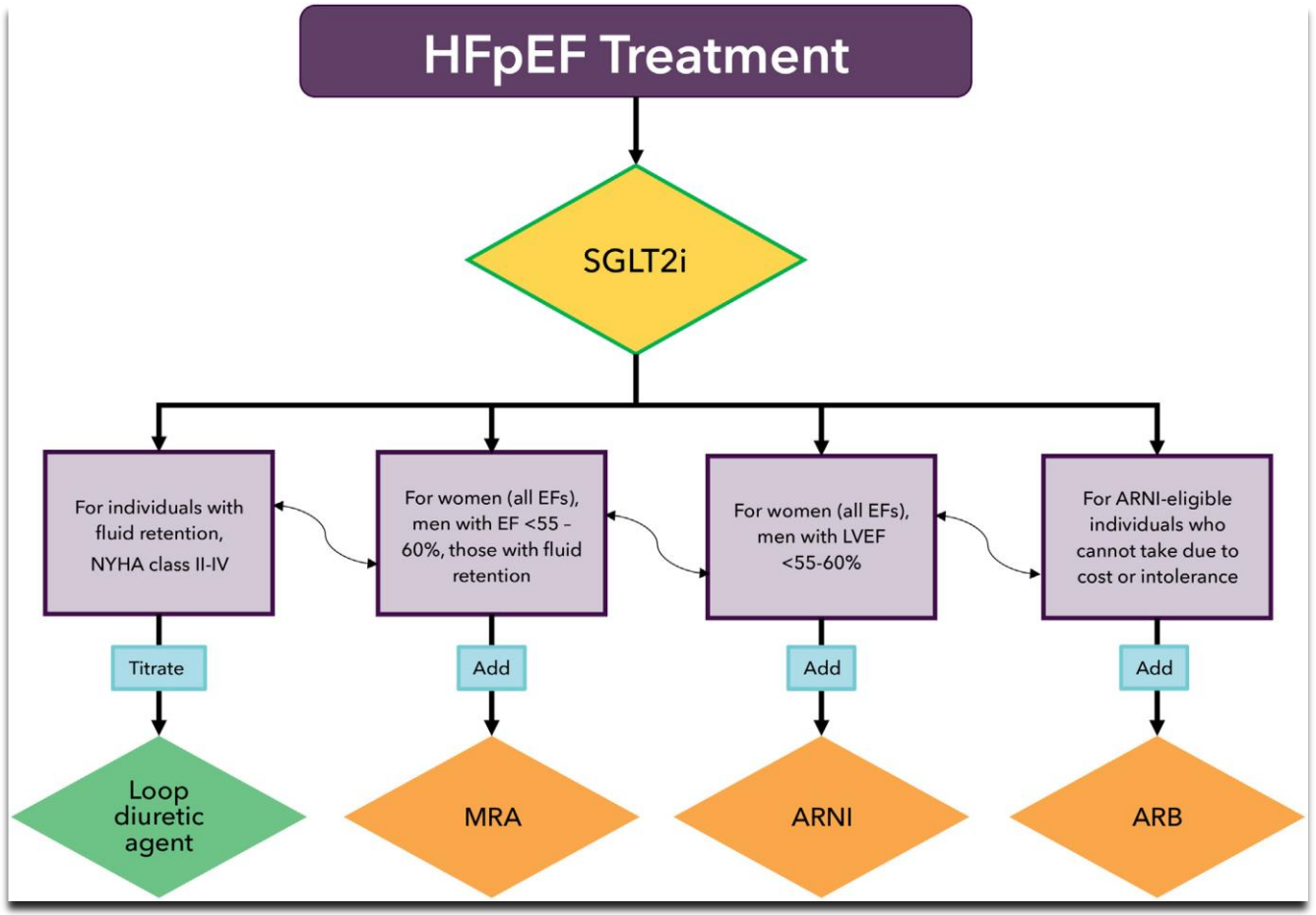


Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c 6,8]	I	A

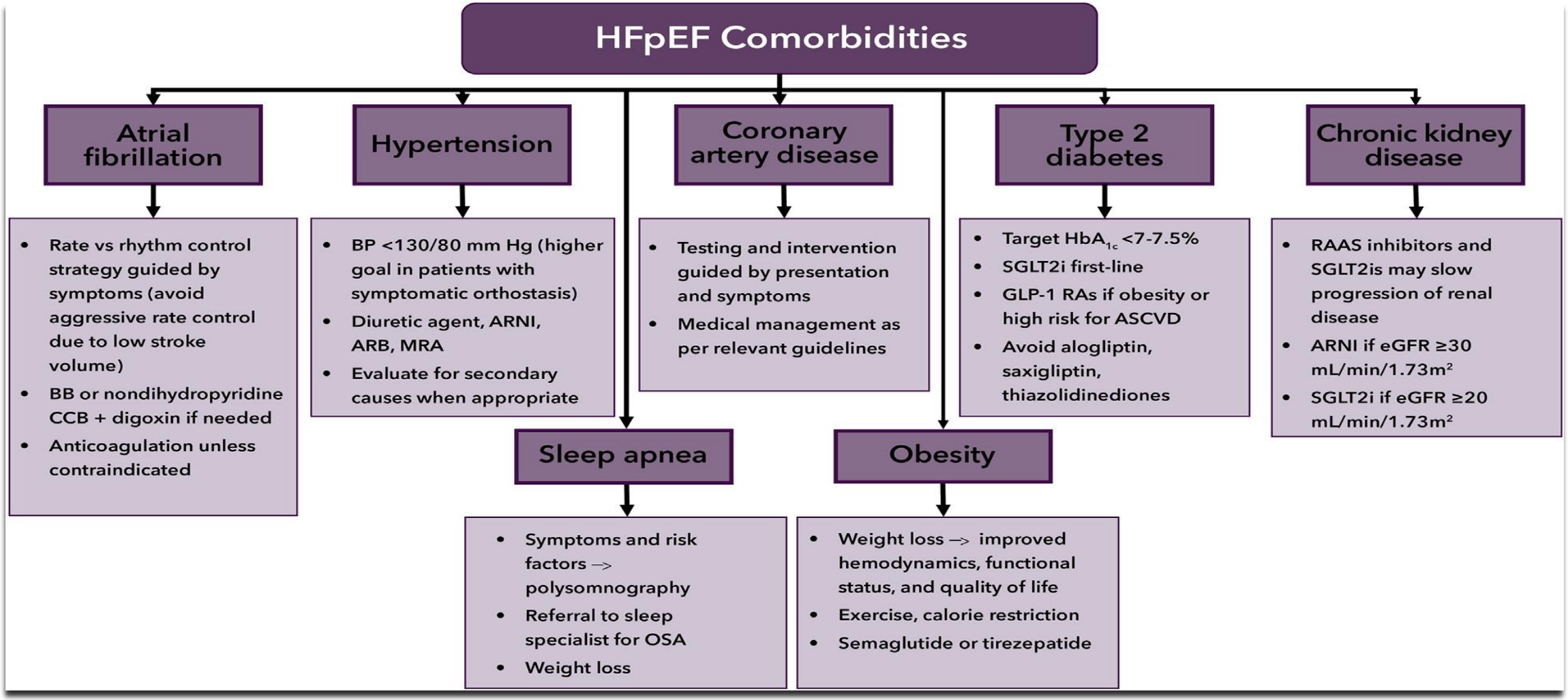
Ref: 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Treatment algorithm for GDMT in HEpEF



Ref : 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure Preserved Ejection Fraction

Management of co-morbidities associated with HFpEF



Ref : 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure Preserved Ejection Fraction

Clinical Evidence

EMPEROR-Preserved

- double-blind, placebo-controlled trial
- randomized 5988 patients
- symptomatic HF (New York Heart Association [NYHA] **class ≥II**) and a left ventricular ejection fraction **(LVEF) of >40%**
- empagliflozin (10 mg orally once daily) or matching placebo
- The second secondary outcome was the rate of decline in the eGFR during double-blind treatment.
- In the main trial, empagliflozin, versus placebo, reduced the risk of the primary composite outcome (13.8% in the empagliflozin group vs. 17.1% in the placebo group.

EMPEROR-Preserved

OUTCOMES

PRIMARY OUTCOMES:

- Death from cardiovascular causes or hospitalization for heart failure-

  13.8% vs.17.1% (HR 0.79; 95% CI 0.69-0.90; P<0.001; NNT=30)

SECONDARY OUTCOMES:

- Hospitalization for heart failure-

  8.6% vs.11.8% (HR 0.71; 95% CI 0.60-0.83; NNT=31)

- Death from cardiovascular causes-

  7.3% vs.8.2% (HR 0.91; 95% CI 0.76-1.09)

n engl j med 385;16 nejm.org October 14, 2021

EMPEROR-Preserved

- Empagliflozin reduced the risk of the **primary composite outcome of cardiovascular death or hospitalization** for HF, the key secondary outcome of **total hospitalizations** for HF, and of **eGFR slope**, in patients with and without CKD.

- The benefit across the primary and key secondary outcomes was consistent across the spectrum of eGFR

- Empagliflozin reduced the reporting of acute kidney injury and slowed the progression to macroalbuminuria overall and across CKD and eGFR categories

- Empagliflozin was well – tolerated in patients with and without CKD

DELIVER

Dapagliflozin in Heart Failure with Mildly Reduced and Preserved Ejection Fraction

Purpose:
To evaluate whether SGLT2 inhibitors (dapagliflozin) are effective in patients with heart failure and more than 40% left ventricular ejection fraction.

Trial Design: This was an international, multicenter, parallel-group, event-driven, randomized, double-blind, placebo-controlled study. N=6,263 patients with heart failure and a left ventricular ejection fraction of more than 40% were randomized in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo.

Primary Endpoint: Time-to-event analysis of a composite of worsening heart failure (defined as unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death [over a median of 2.3 years].

Other Endpoints: Total number of worsening heart failure events and cardiovascular death, death from any cause, and change in total symptoms score of KCCQ at 8 months.

Results	Dapagliflozin	Placebo	P-value
Primary Composite Outcome – no.(%): Time to first occurrence of: 1) CV death; 2) Hospitalization for HF; 3) Urgent visit for HF	512 (16.4)	610 (19.5)	< 0.001
Total # of worsening HF events + Death	815	1057	< 0.001
Death from any cause – no. (%)	497 (15.9)	526 (16.8)	NA
Change in total symptom score of KCCQ at 8 months	Win ratio, 1.11; 95% CI, 1.03-1.21; P=0.009		

Results: Among individuals with heart failure and a mildly reduced or preserved ejection fraction, **dapagloflozin reduced the combined risk of worsening heart failure or cardiovascular death**.

Presented by: Dr. Scott Solomon for the DELIVER Investigators

Recommendation for SGLT2 inhibitors in HFmrEF and HFpEF

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c 6,8]	I	A

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c 6,8]	I	A

Cardiac Rehabilitation

- All patients with HF should be encouraged to enrol in a multidisciplinary care cardiac rehabilitation programme

Palliative care

- Referral to a palliative care specialist should be considered

- Palliative care can provide
  - improved quality of life through symptom management
  - assistance with medical decision-making
  - care that addresses emotional and spiritual needs

Take home message …

- Guideline-directed medical therapy (GDMT) is the mainstay of treatment for initial and chronic management of HFrEF
- GDMT has been shown to improve the overall survival rate of patients living with HFrEF
- Four pillars of heart failure: ARNI, Beta blockers, MRA, SGLT2 inhibitors
- Initiation and optimization of medical therapy with proper reassessment for individualized care
- Timely referral for advanced heart failure management
- Holistic approach : patient and family education, exercise and rehabilitation programme , psychosocial support , palliative care

Thank you for your attention

SGLT2 inhibitors in T2DM, Heart Failure and Kidney Disease Guide

Indications

- **Canagliflozin: For T2DM** start with 100mg OD, increase to 300mg OD if needed and if eGFR ≥ 60. For eGFR 30-60 use 100mg. If eGFR < 30, continue only if already on it.
  For DKD use 100mg OD (initiate only if uACR ≥ 25mg/mmol* and eGFR ≥ 30, continue to ESKD).

- **Dapagliflozin: For T2DM** use 10mg OD, in severe hepatic impairment start with 5mg.
  For CKD without diabetes use 10mg OD (initiate only if uACR ≥ 25mg/mmol* and eGFR ≥ 25, continued to ESKD).
  For CKD with diabetes use 10mg OD (eGFR ≥ 25 and continued to ESKD).
  For HFrEF with or without diabetes use 10mg OD. (Initiate only if LVEF < 40%, NYHA Class II-IV and eGFR ≥ 20#. Stop if eGFR < 20).

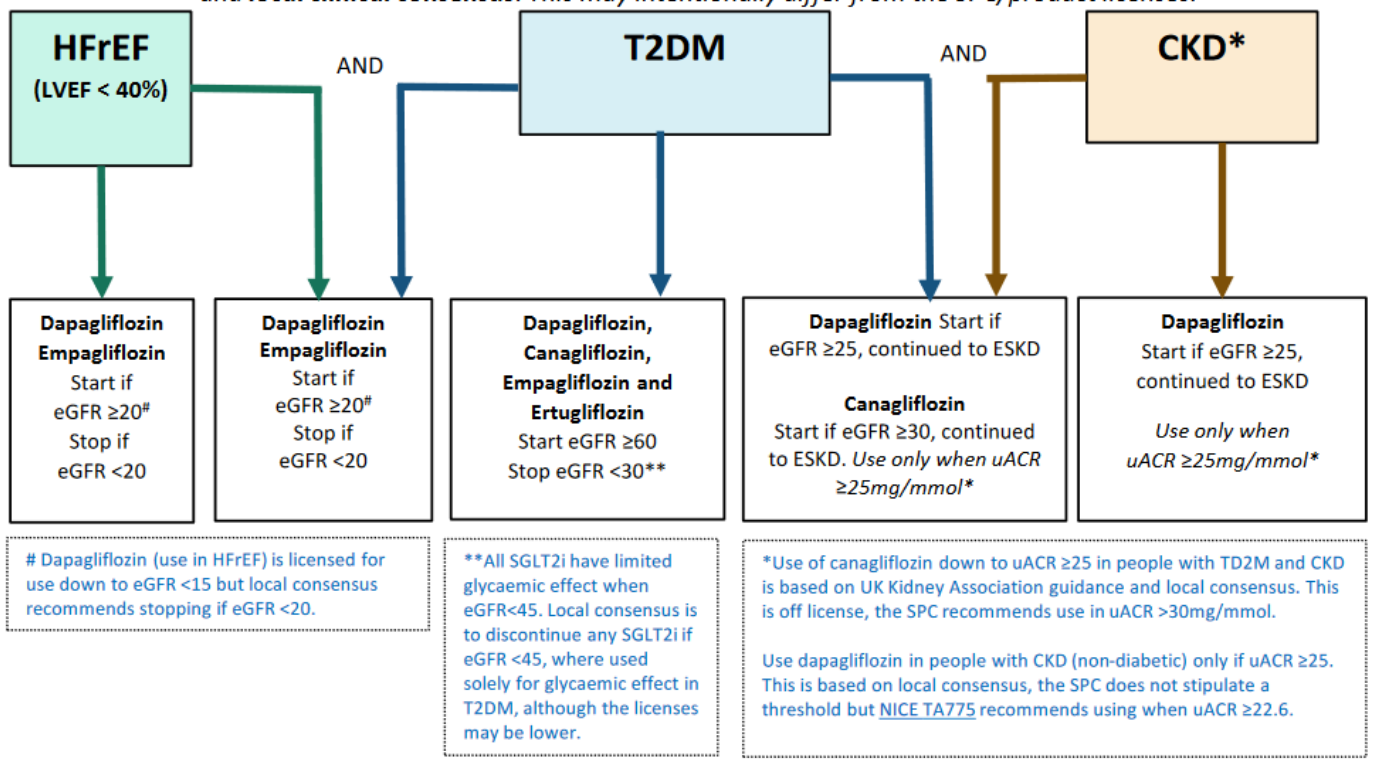
- **Empagliflozin: For T2DM** start with 10mg, increased to 25mg OD if needed and eGFR ≥ 60.
  For T2DM + CVD: Initiate 10mg where eGFR 30-60 but do not increase dose above 10mg. Stop if eGFR < 30.
  For HFrEF with or without diabetes: Use 10mg OD (initiate only if LVEF < 40%, NYHA II-IV and eGFR ≥ 20). Do not increase dose over 10mg. Stop if eGFR < 20 for HFrEF. Empagliflozin is not currently licensed for CKD.

- **Ertugliflozin**: **For T2DM** start with 5mg OD increasing to 15mg OD if needed and eGFR ≥ 60. Stop if eGFR < 45. Not currently licensed for CKD and/or heart failure.

- ***NB**: Most SGLT2 inhibitors are 'green' on formulary for use in T2DM and CKD (within the stated indications). Use in HFrEF is 'amber' specialist recommendation only.*

Algorithm for renal considerations based on reason for SGLT2i initiation

*Renal thresholds used in this guidance reflects the **evidence base** available at the time of publication (February 2022) and **local clinical consensus**. This may intentionally differ from the SPC/product licenses.*



Dapagliflozin (use in HFrEF) is licensed for use down to eGFR <15 but local consensus recommends stopping if eGFR <20.

**All SGLT2i have limited glycaemic effect when eGFR<45. Local consensus is to discontinue any SGLT2i if eGFR <45, where used solely for glycaemic effect in T2DM, although the licenses may be lower.

*Use of canagliflozin down to uACR ≥25 in people with TD2M and CKD is based on UK Kidney Association guidance and local consensus. This is off license, the SPC recommends use in uACR >30mg/mmol.

Use dapagliflozin in people with CKD (non-diabetic) only if uACR ≥25. This is based on local consensus, the SPC does not stipulate a threshold but NICE TA775 recommends using when uACR ≥22.6.

CAUTIONS

- Prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections
- History of organ transplantation
- History of recurrent mycotic genital tract infection
- At risk of significant volume depletion and hypotension
- At risk of DKA: HbA1c >86mmol/mol (10%) or low beta cell function reserve (e.g., T2DM with low C-peptide levels, LADA, history of pancreatitis, Type 3c DM, severe dehydration, sudden reduction in insulin, acute illness, surgery, previous episode of DKA, very low carbohydrate/ketogenic diet)

CONTRAINDICATIONS

- eGFR <15ml/min/1.73m2
- Receiving dialysis
- Polycystic kidney disease
- Patient with a solid organ transplant and/or receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy the use of an SGLT2i is outside the licensed indication (agreed by local consensus)
- Type 1 diabetes mellitus
- Previous DKA
- Pregnancy or breast feeding

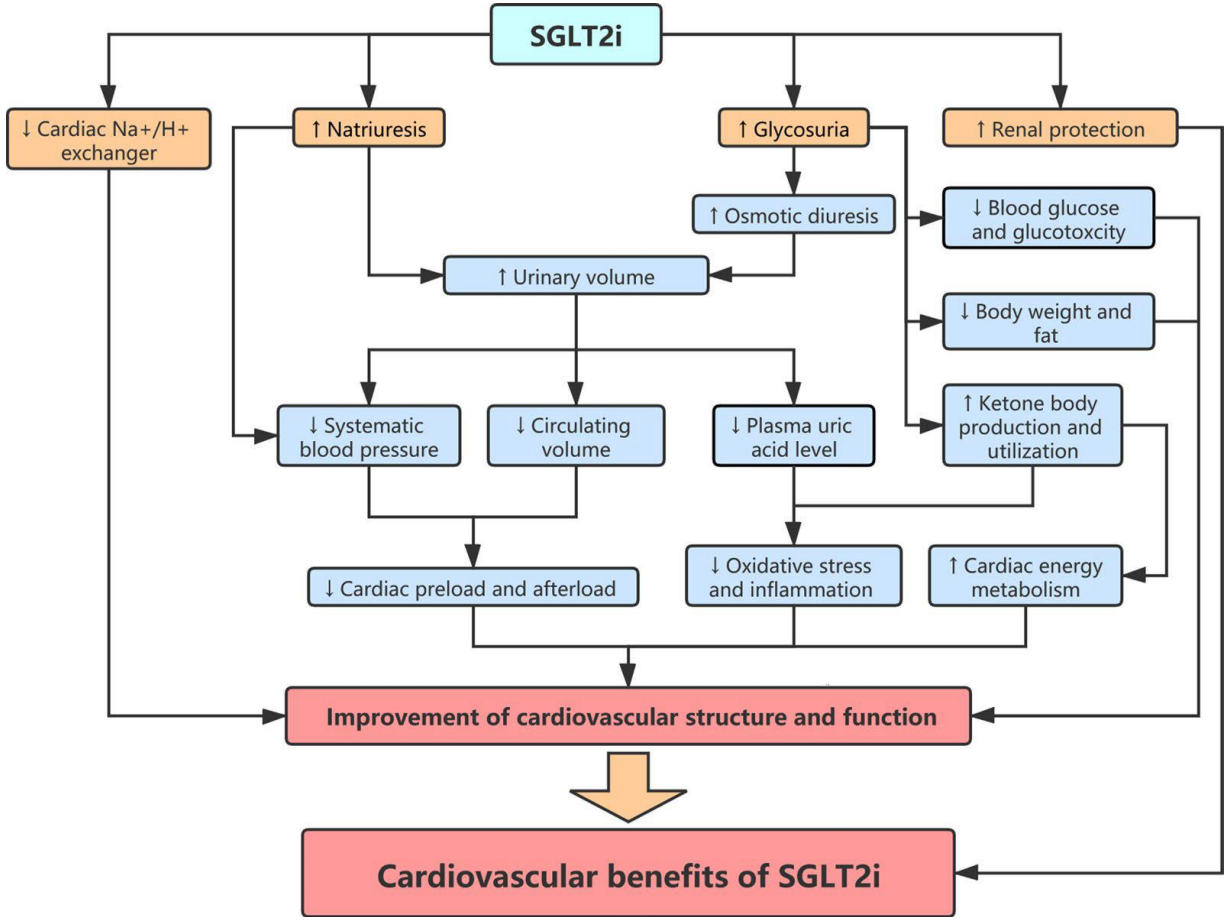
COUNSELLING:

- Counsel patients about the risk/signs of DKA. This risk is increased during periods of intercurrent illness (see advice in sick day guidelines on the APC formulary). Patients should speak to their healthcare professional if acutely unwell or before starting any ketogenic/low carb diet.
- Advise about the importance of routine preventive foot care and adequate hydration
- Counsel patients on risk of Fournier's gangrene and candida infections.

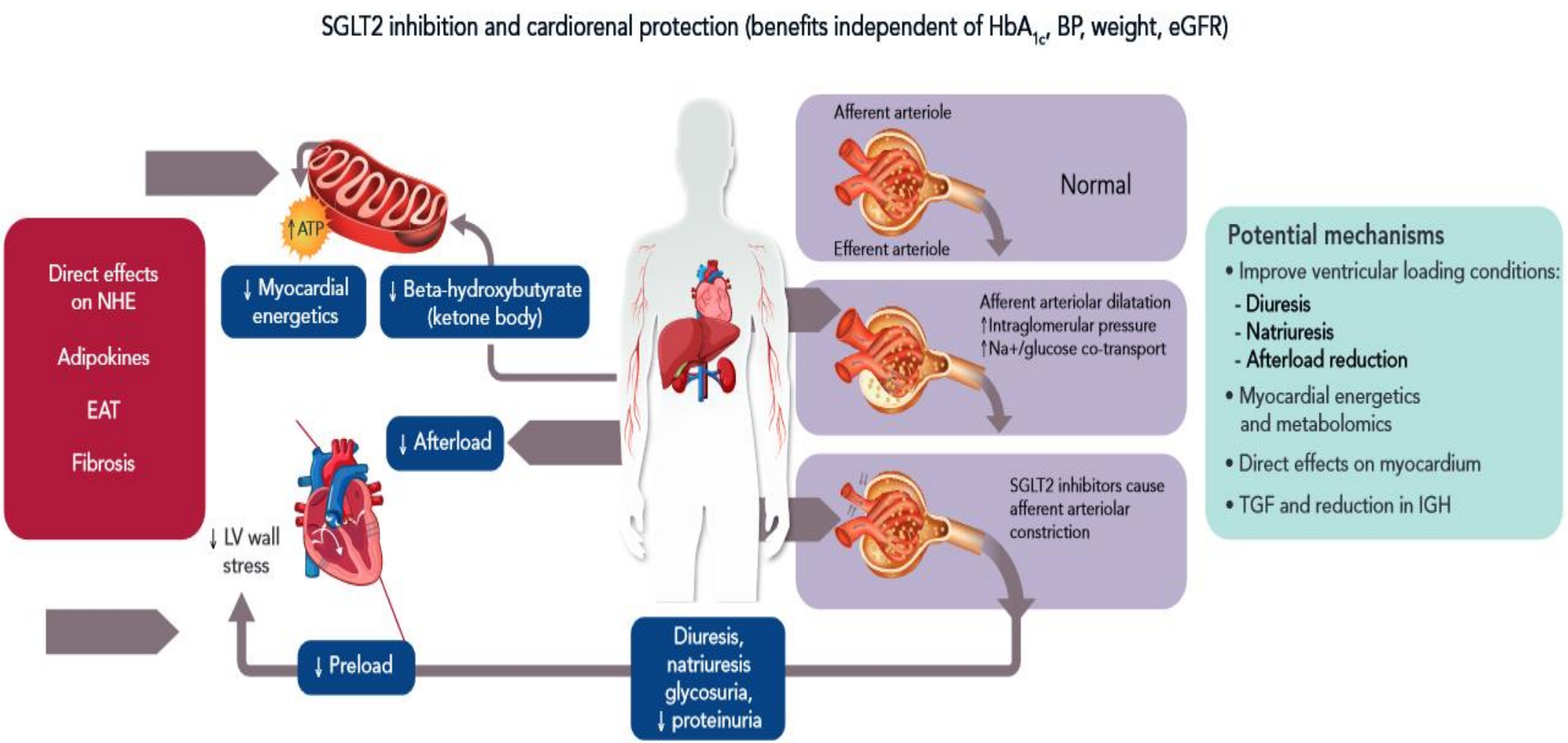
Types of heart failure according to LVEF

Type of Heart Failure according to LVEF	Criteria
HFrEF (Heart failure with reduced EF)	LVEF **≤ 40 %**
HF imp EF (Heart failure with improved EF)	Previous LVEF ≤ 40 % and follow up measurement of LVEF > 40 %
HF mr EF (Heart failure with mildly reduced EF)	LVEF **41 – 49 %**
HFpEF (Heart failure with preserved EF)	LVEF **≥ 50 %**

Cardiovascular benefits of SGLT2 inhibitors



Proposed mechanisms of cardiovascular benefits of SGLT2 inhibitors



Sodium–Glucose Co-transporter 2 Inhibitors in Heart Failure: Recent Data and Implications for Practice

Giuseppe Rosano,[1] David Quek[2] and Felipe Martínez[3]

- The Universal Definition of HF requires
  - symptoms and/or signs of HF, caused by structural/functional cardiac abnormalities

and at least 1 of the following:

1) elevated natriuretic peptides
2) objective evidence of cardiogenic pulmonary or systemic congestion.

HFpEF

- HFpEF: Clinical diagnosis of HF and LVEF $\geq$ 50%
- Not attributable to an underlying cause such as an infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF

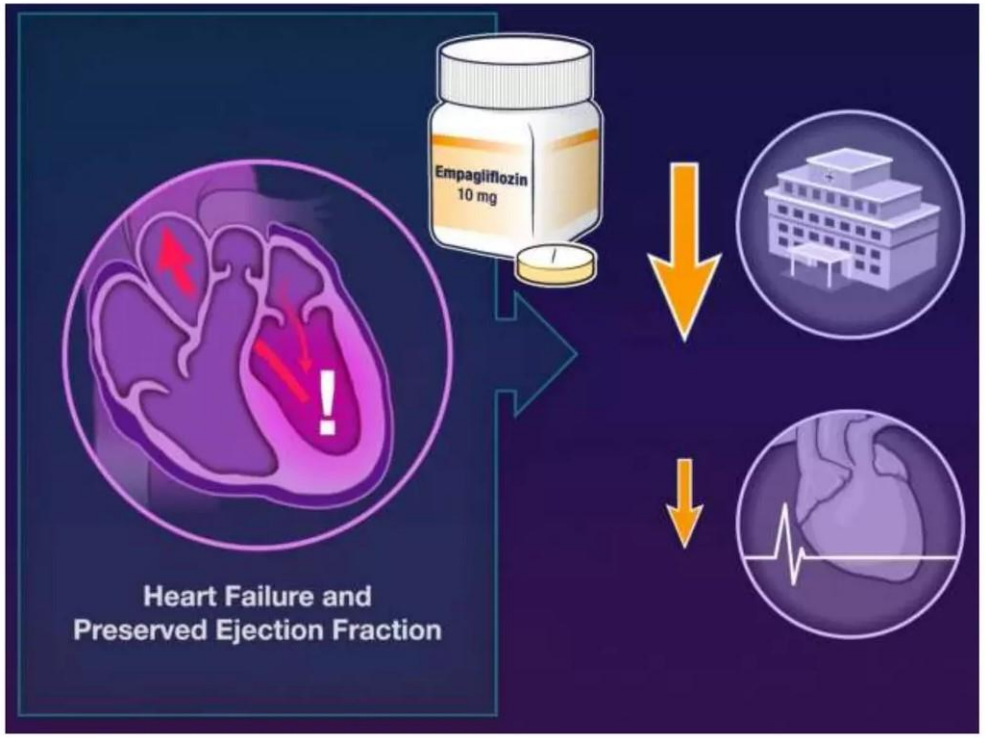
HFpEF mimics

- HFpEF mimics: Clinical diagnosis of HF and LVEF $\geq$ 50%
- with a primary noncardiac cause (kidney or liver disease)
- or an underlying cardiac cause (infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF).

EMPEROR-Preserved

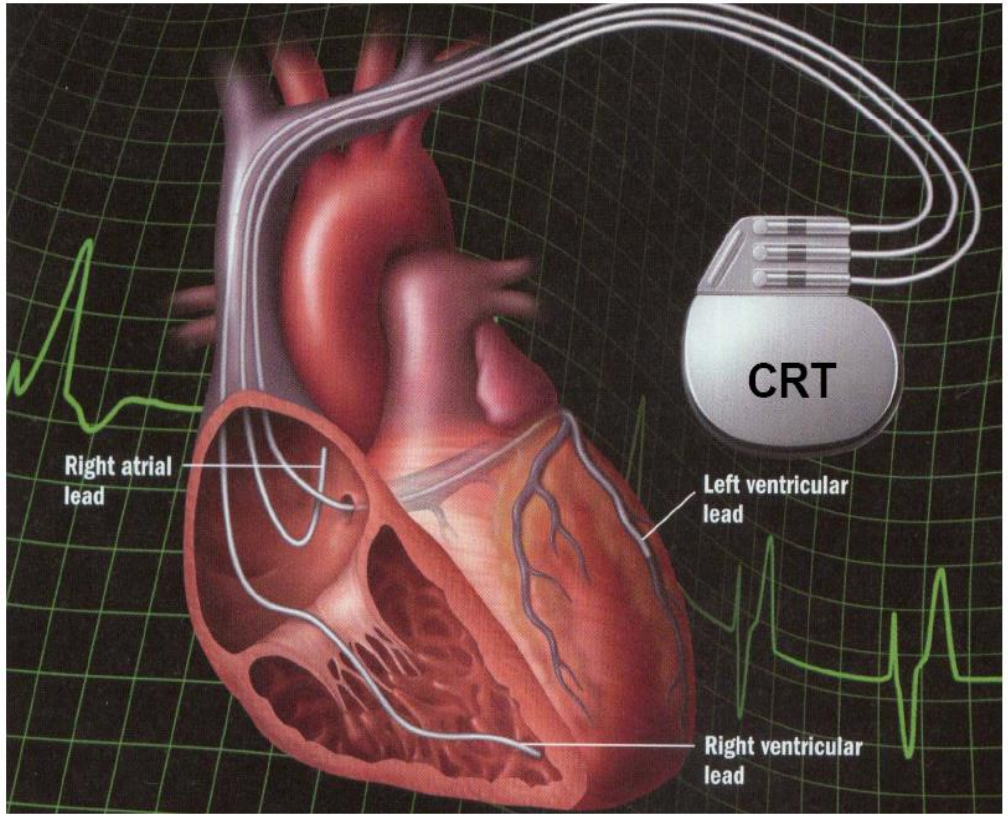
- Among adults with heart failure with mid-range or preserved EF (LVEF > 40 %), Empagliflozin decreased the risk of cardiovascular death or heart failure hospitalization

- This benefit was **mainly driven by fewer heart failure hospitalization.**



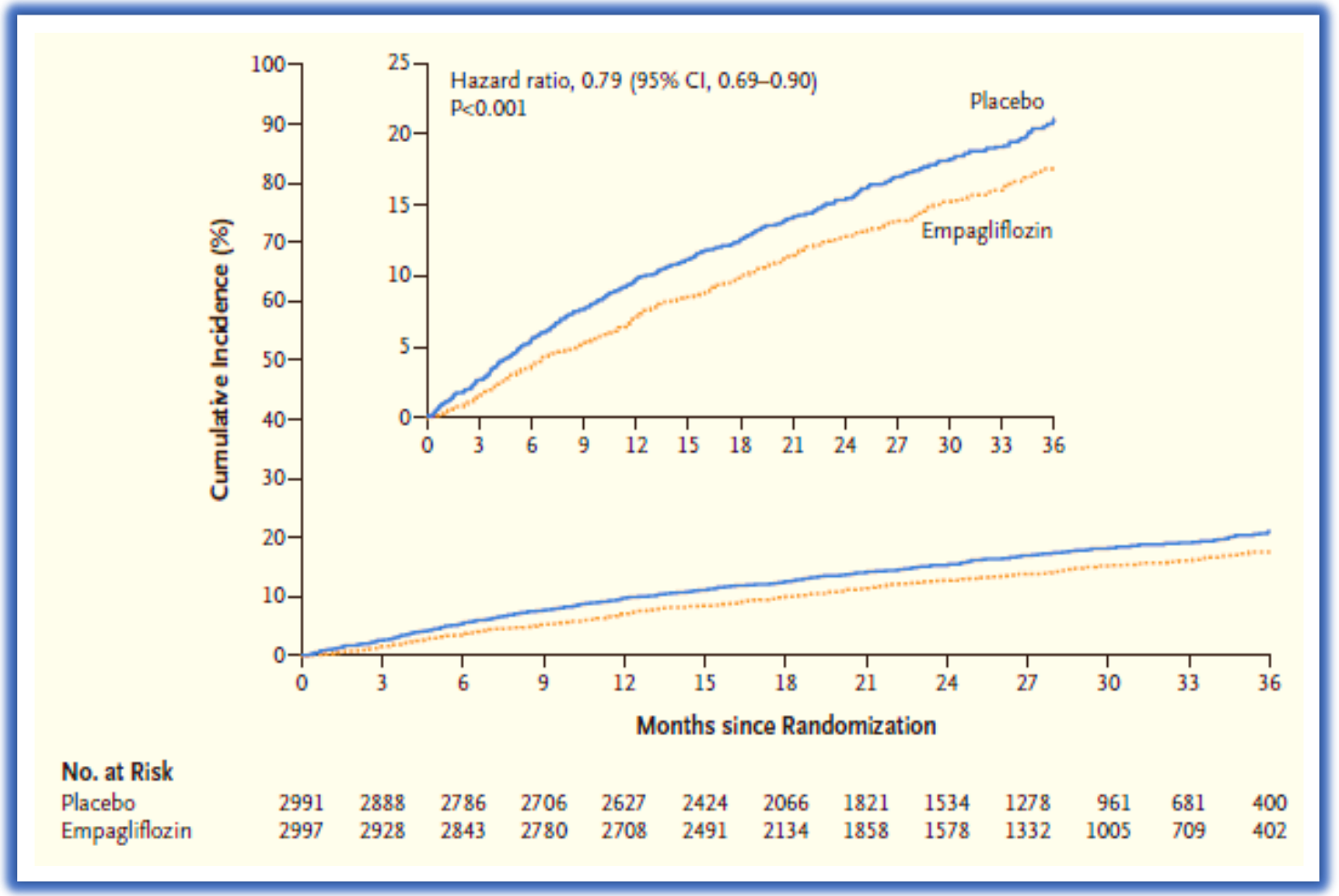
n engl j med 385;16 nejm.org October 14, 2021

Cardiac Resynchronization Therapy with defibrillation (CRTD)



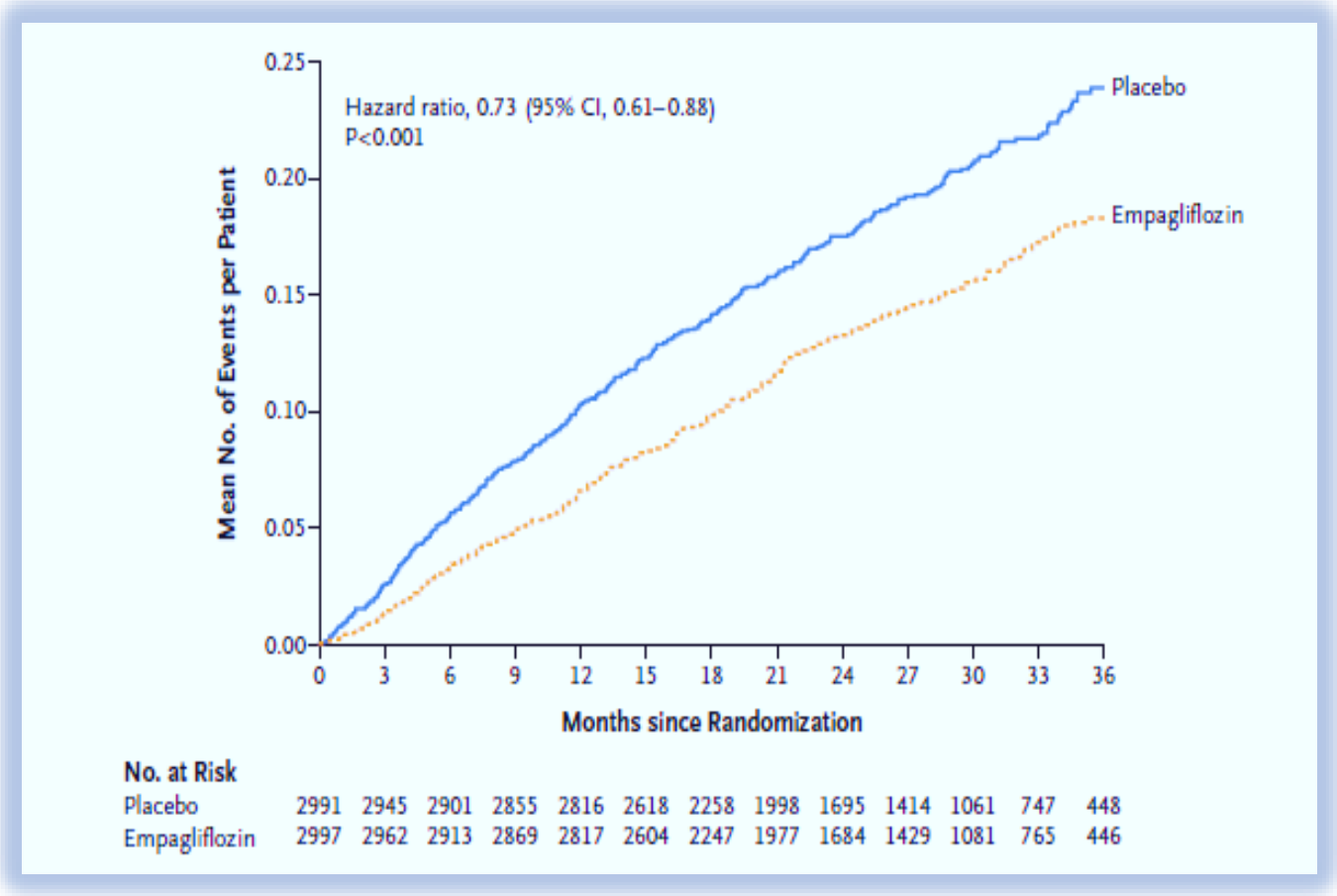
EMPEROR-Preserved

Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.



EMPEROR-Preserved

The first secondary outcome was the occurrence of all adjudicated hospitalizations for HF including first and recurrent events.



PARADIGM – HF Trial was stopped early
Median follow up 27 months

	LCZ 696	Enalapril	Hazard ratio	P value
Primary outcome	914 pts (21.8%)	1117 pts (26.5%)	0.84	<0.001
deaths	711(17.0%)	835 pts (19.8%)	0.84	<0.001
CV death	558 (13.3%)	693(16.5%)	0.80	<0.001
Risk of hospitalization due to HF	Reduction by 21%			<0.001
Symptoms and physical limitations of HF				=0.001