Standard Care of Patients with CHF

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HF Has a Significant Impact on Patients, HCPs, and Healthcare Systems

Highly prevalent condition

> 60 million people worldwide have HF[a]

This is more than 5× the number of cancer patients globally[b]

1 in 5

lifetime risk of developing HF for people at 40 years old[c]

Associated with high rates of morbidity and mortality

50% of HFrEF patients will **die within 5 years** of diagnosis[d]

Despite advances in management, HF remains as **malignant as some common cancers** (prostate, bladder, and breast)[e]

Poses a significant strain on healthcare system

HF is the **#1 reason for hospitalisation** in patients aged >65 years globally[f]

24% median 30-day HF readmission rate[g]

60% of HF patients rehospitalised for HF within 1 year[h]

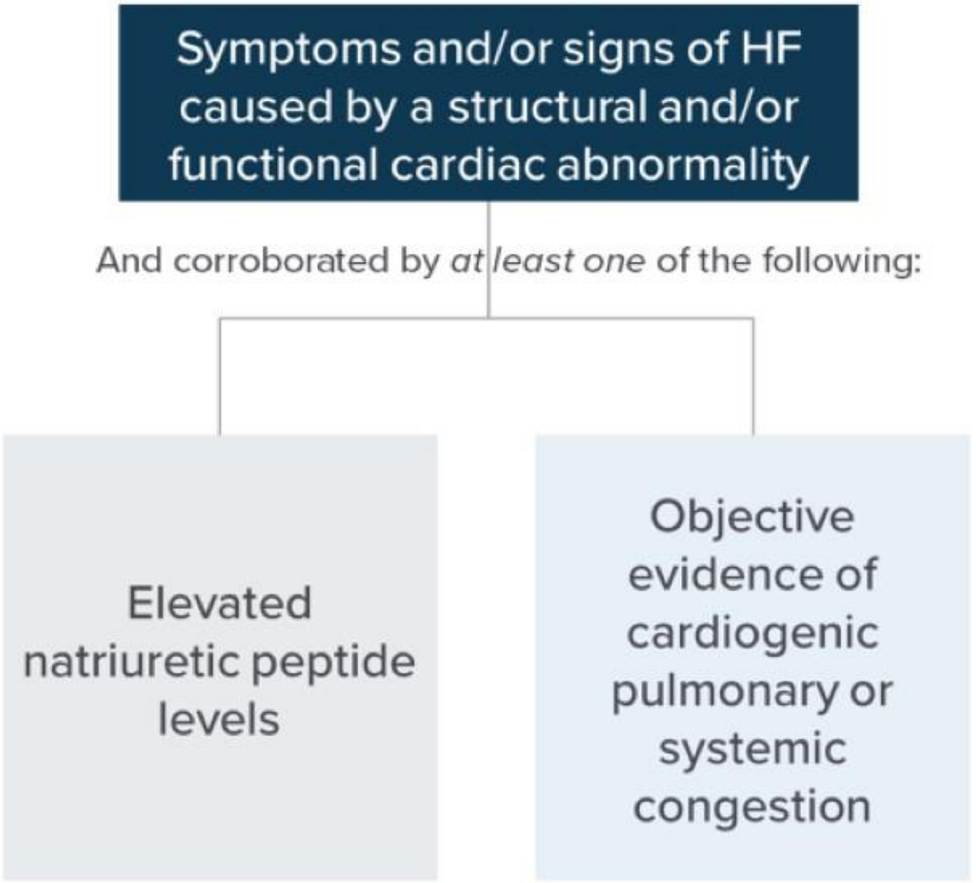
1 in 3 of HF patients die within 1 year of hospitalization for HF[i]

a. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211-1259; b. Sung H, et al. *CA Cancer J Clin*. 2021. [Epub ahead of print]; c. Mozaffarian D, et al. *Circulation*. 2016;133:e38-e360; d. Benjamin EJ et al. *Circulation*. 2019;139:e56-e528; e. Mamas MA et al. *Eur J Heart Fail.* 2017;19:1095-1104; f. Maggioni AP et al. *Eur J Heart Fail*. 2016;18:402-410; g. Krumholz HM, et al. *Circ Cardiovasc Qual Outcomes*. 2009;2:407-413; h. Chun S, et al. *Circ Heart Fail.* 2022;5:414-421; i. Chen J, et al. *JAMA*. 2011;306:1669-1678.

Universal Definition of HF

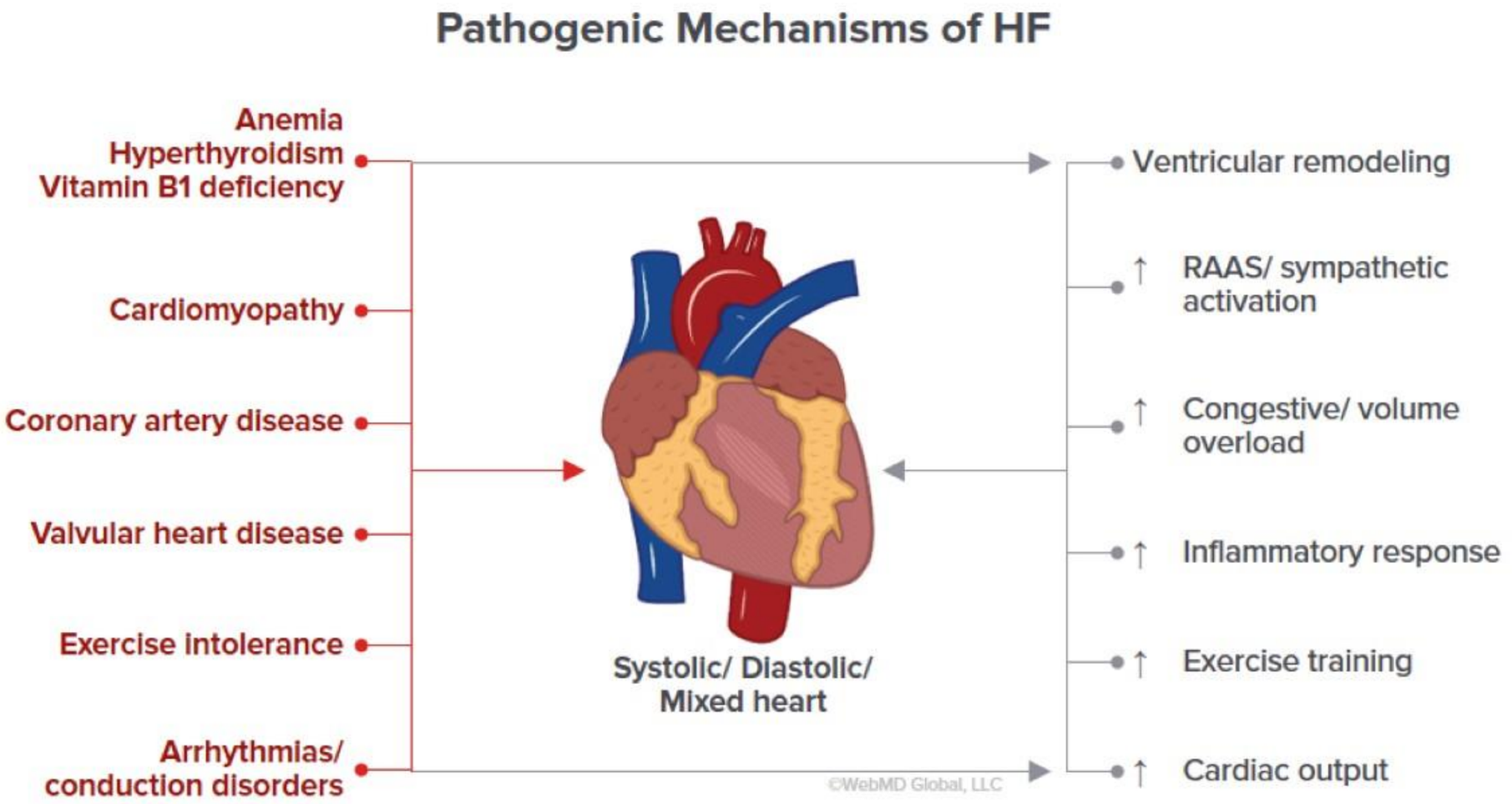
Definition

- **HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion**



Bozkurt B, et al. Eur J Heart Fall. 2021;23:352-380.

Heart Failure: What Is the Etiology?



Inamdar AA, et al. J Clin Med. 2016;5:1-28

Making the HF Diagnosis and Starting Treatment

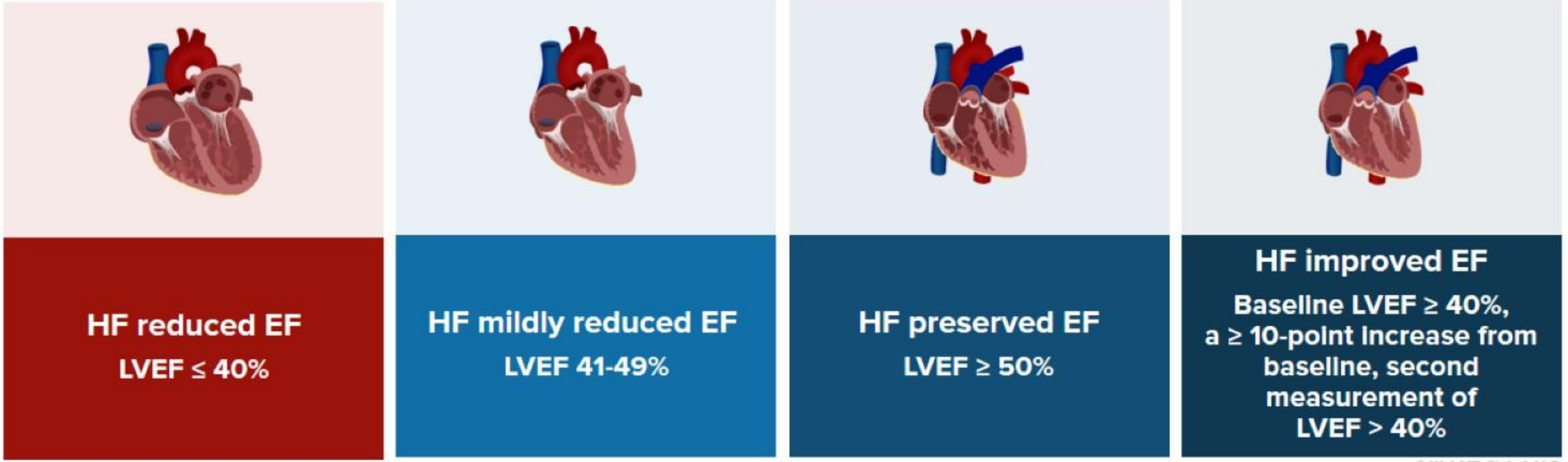
Common Challenges:

- Treatment of HF is independent of the etiology
- HF treatment is often focused on blocking neurohormonal changes with neurohormonal antagonists and modulators. Workup must be complete
- Catastrophic events such as ACS must be ruled out first

New Classification of HF According to LVEF

HFimpEF

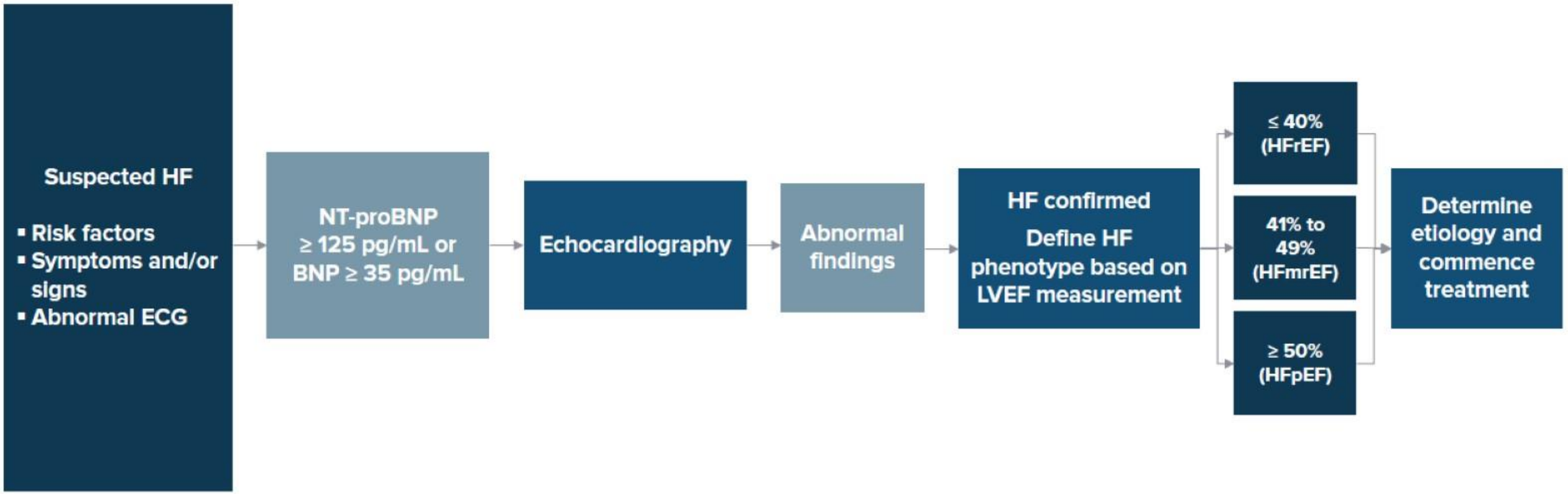
- New classification/category
- Encourages use of GDMT that is beneficial in patients with HFrEF
- Patient may have improvement in LVEF, but does not have HFpEF



HFImpEF, heart failure with improved ejection fraction.

Bozkurt B, et al. Eur J Heart Fail. 2021;23:352-380.

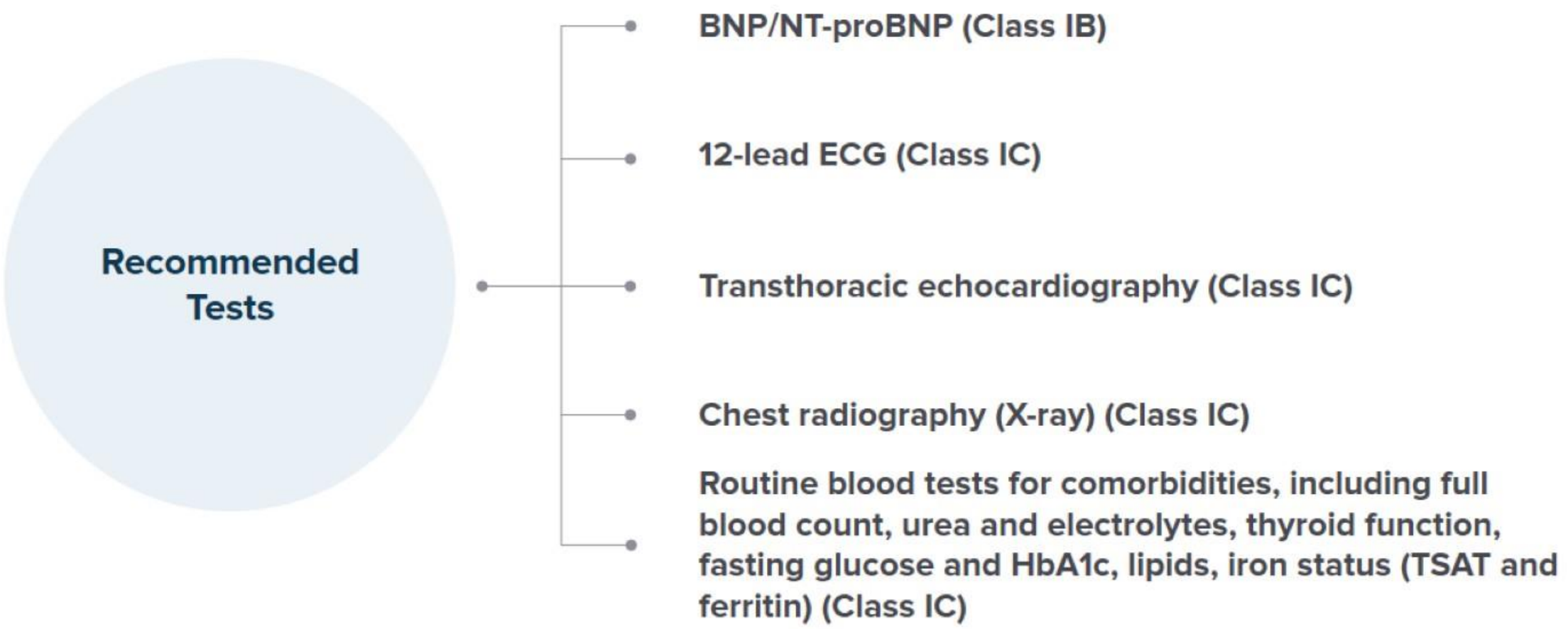
2021 ESC Guidelines: Diagnostic Algorithm for HF



ECG, electrocardiogram; ESC, European Society of Cardiology; NT-proBNP, N-terminal pro b-type natriuretic peptide.

McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726.

2021 ESC Guidelines: Patients With Suspected HF



HbA1c, glycated haemoglobin; TSAT, transferrin saturation.

McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726.

The Pharmacological Story

SNS — X — **β blockers**

Adrenaline, Noradrenaline } α_1, β_1, β_2 receptors

Vasoconstriction
- Heart rate ↑
- Contractility ↑
- RAAS activity ↑
- Vasopressin ↑

NPS

NP receptors ← Natriuretic Peptides

Vasodilatation
- ↓ Blood pressure
- ↓ Sympathetic Tone
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Hypertrophy
- ↓ Fibrosis
- ↑ Natriurersis/Diuresis

Natriuretic Peptides → Neprilysin → Inactive fragments

Neprilysin — X — **ARNIs**

RAAS — X — **RAAS Inhibitors ACEI, ARB, MRA**

Angiotensin II → AT_1 receptor

ARNIs — X

Vasoconstriction
- Blood pressure ↑
- Sympathetic Tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis ↑

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NP, natriuretic peptide; NPS, natriuretic peptide system; RAAS, renin angiotensin aldosterone system.
MacDonald PS, et al. Clin Ther. 2015;37:2199-2205.

PARADIGM-HF Study

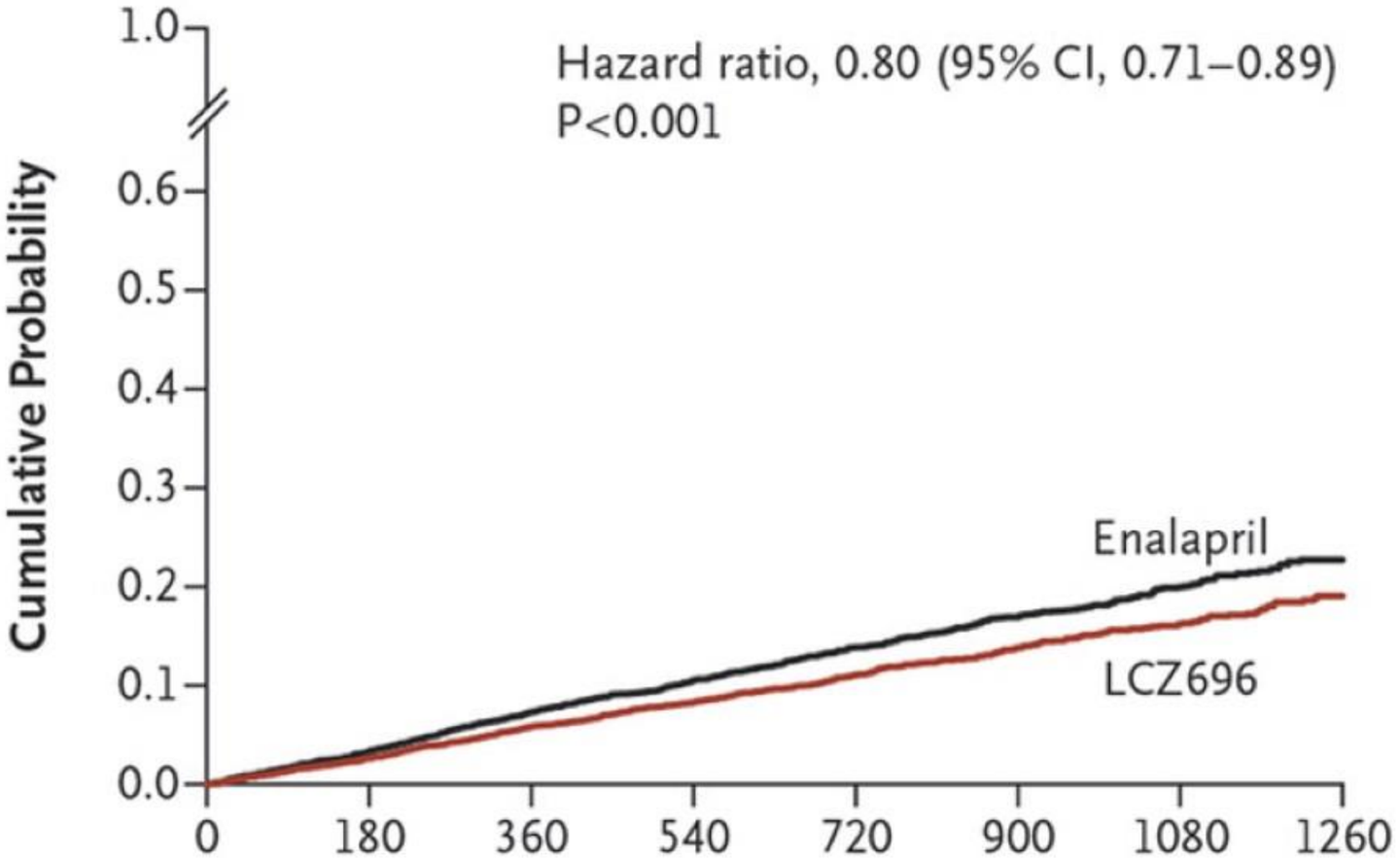
~ 8400 patients

- EF ≤ 35%
- One HF hosp or ↑ BNP

Sacubitril/valsartan vs enalapril

Outcomes

- CV deaths: 17% → 13%
- HF hosp: 16% → 13%

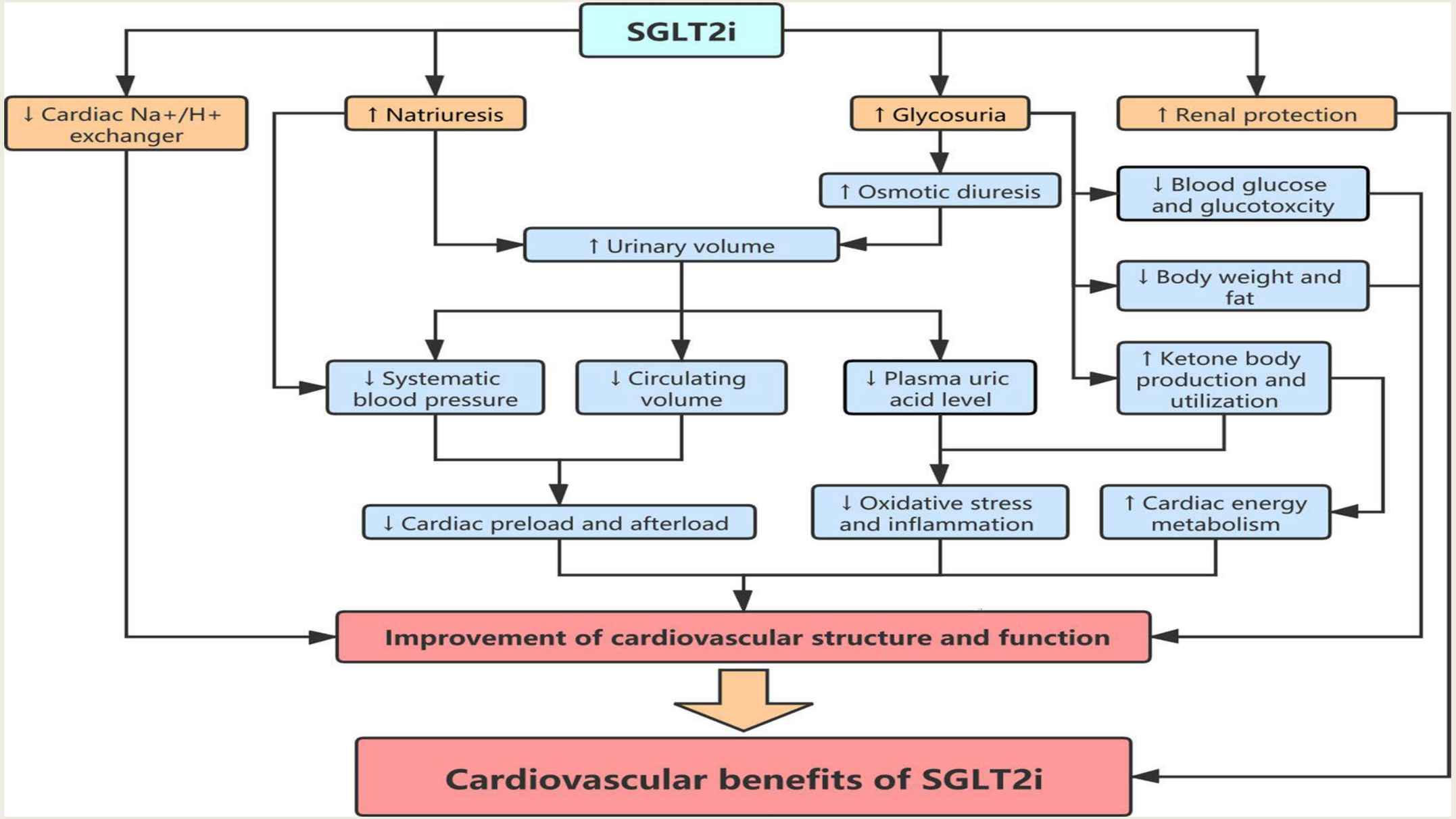


BNP, B-type natriuretic peptide; CV, cardiovascular.
McMurray J, et al. N Engl J Med. 2014;371:993-1004.

Cardiovascular protection mechanisms of SGLT2 inhibitors

- SGLT2 inhibitors block transport of glucose by SGLT2 competing with glucose for binding sites
- They reduce the T_{max} of glucose reabsorption in the proximal tubule, leading to urinary glucose excretion at a lower threshold concentration
- Multiple direct & indirect mechanisms
- Improve many aspects : hemodynamics, metabolism, oxidative stress & inflammation
- Cardiovascular benefits are not related to anti-hyperglycemic effect of SGLT2i.

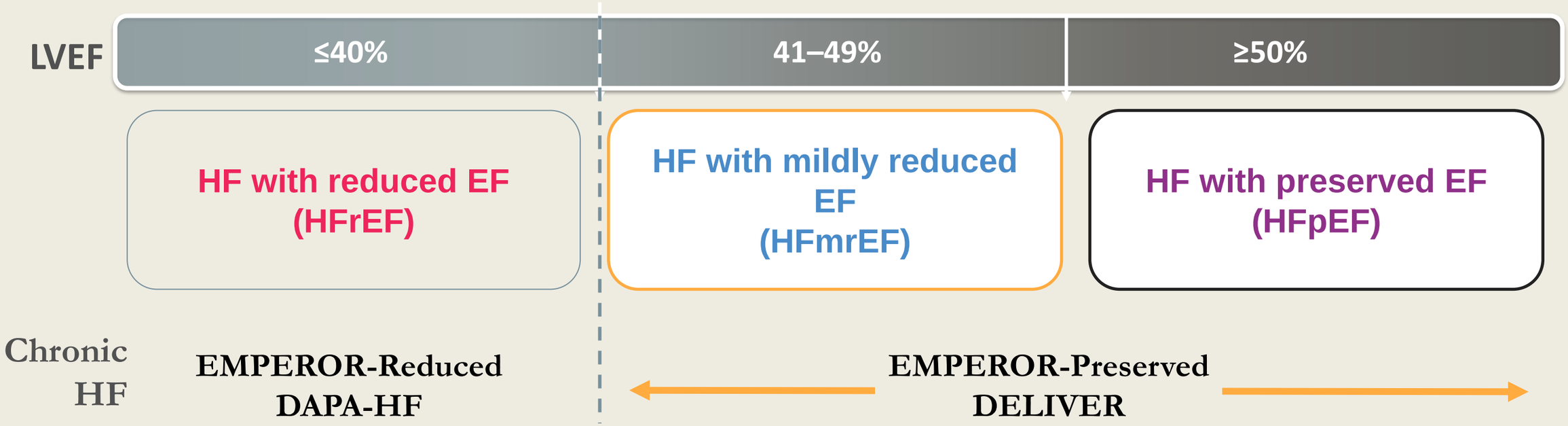
New Pharmacological Story



Cardiovascular benefits

- Glycemic control & attenuation of glucotoxicity
- Natriuresis, diuresis & reduction in plasma volume
- Reduction in BP
- Amelioration of endothelial dysfunction & vascular stiffness
- Improvement of cardiac energy metabolism
- Inhibition of cardiac Na+/H+ (attenuation of cardiac remodeling & fibrosis)
- Improvements in cardiac structure & function
- Attenuation of inflammation
- Reduction in serum uric acid level

SGLT2 inhibitors across a broad range of patients with HF, regardless of ejection fraction



Reduce HF hospitalization, CV death, worsening HF

EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.

1. Packer M, et al. N Engl J Med. DOI: 10.1056/NEJMoa2022190; 2. Anker S *et al. N Engl J Med*. 2021; DOI: 10.1056/NEJMoa210703

2021 ESC HF Guidelines
Therapeutic Algorithm

Early administration of 4 classes of drugs: ACEi/ARNi, beta-blockers, MRA, and SGLT2 inhibitors

Improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF ➔ cornerstone therapies

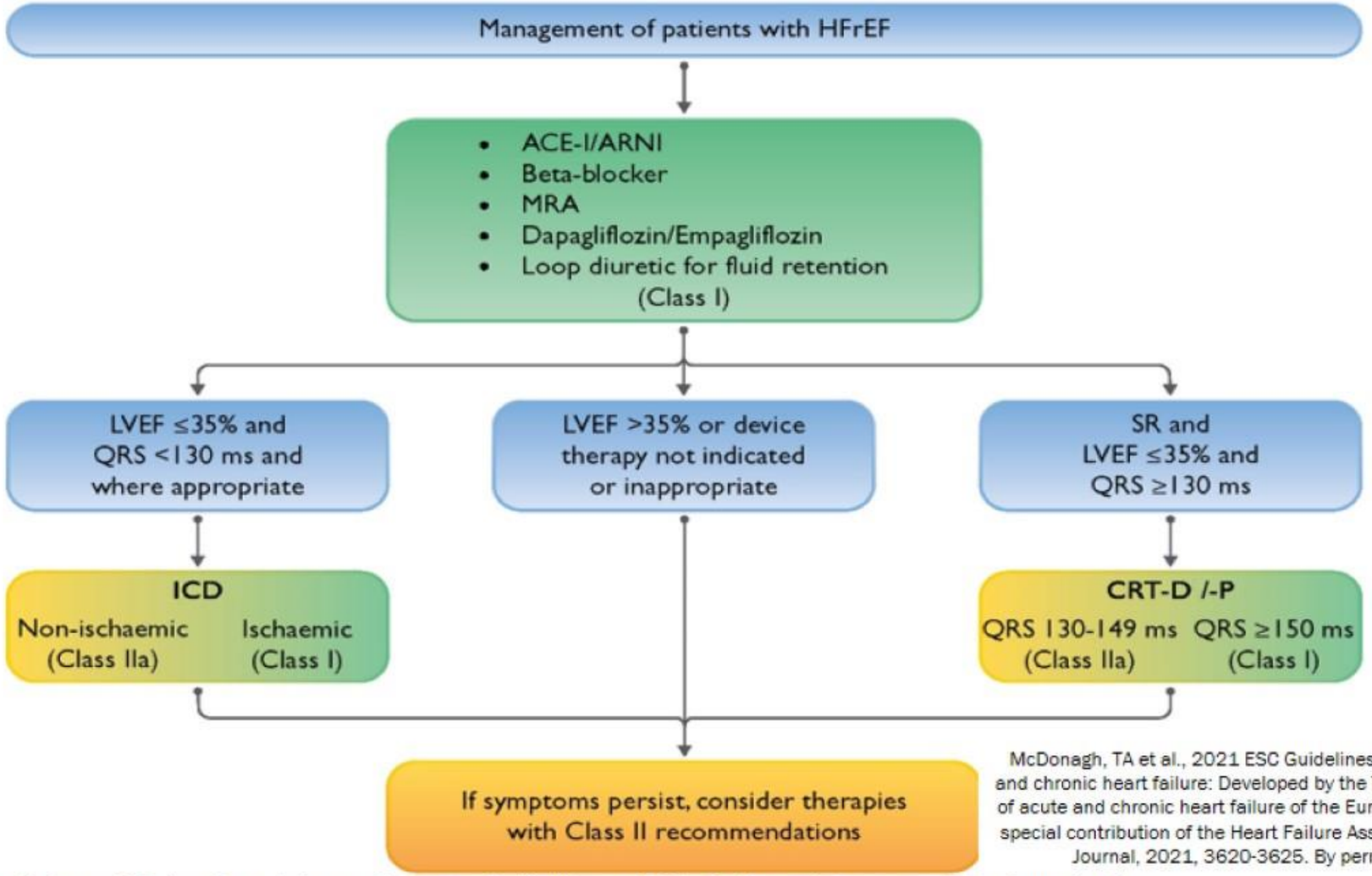
Should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible)

When added to

ACEi/ARNi/BB/MRA reduced the risk of CV death and worsening HF in HFrEF

ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction.
McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726.

ESC 2021 Therapeutic Algorithm of Class I Therapy Indications for HFrEF



McDonagh, TA et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, 2021, 3620-3625. By permission of Oxford University Press.

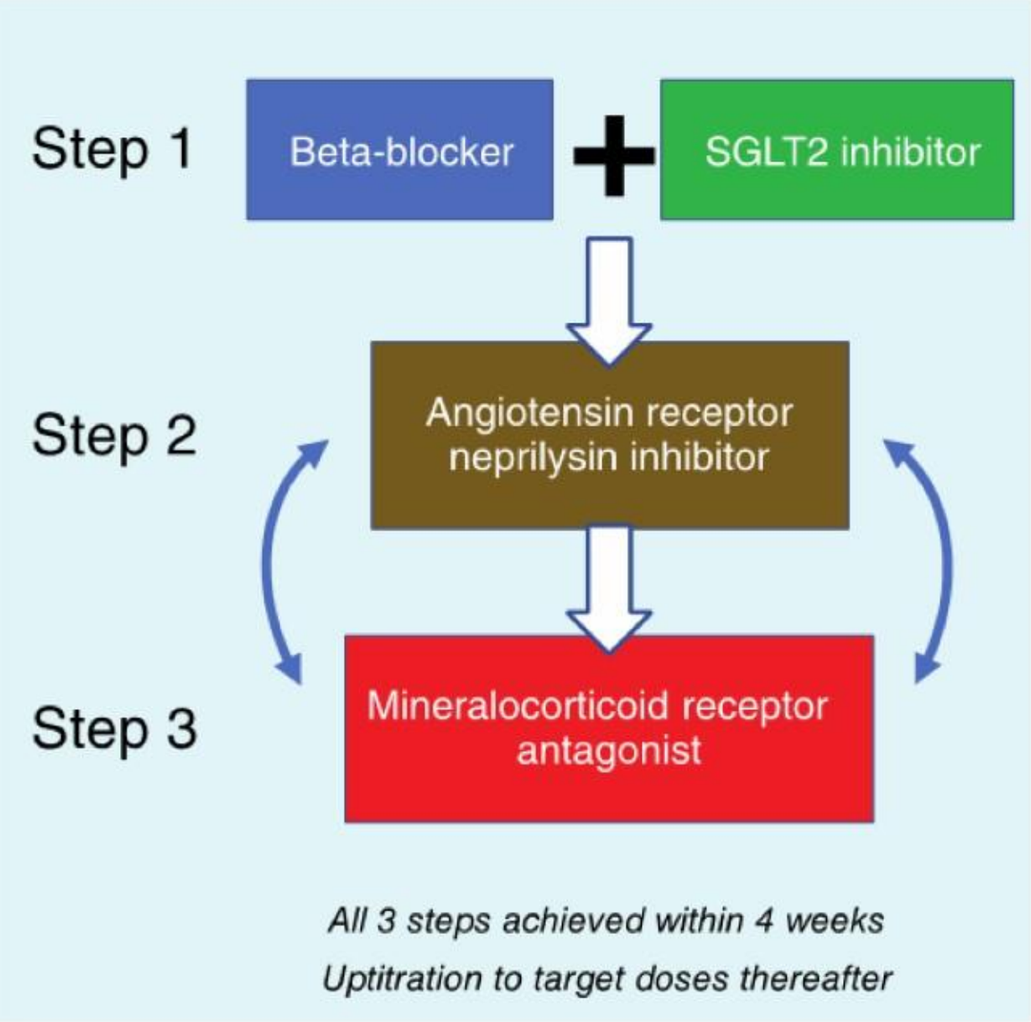
ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; QRS, Q, R, and S waves; SR, sinus rhythm.
McDonagh TA, et al; for the ESC Scientific Document Group. Eur Heart J. 2021;42:3599-3726. Erratum in: Eur Heart J. 2021 Oct 14.

How Should I Consider the Order/Sequence of Drugs?

BP	• Less BP reduction with SGLT2 inhibition and an MRA vs sacubitril/valsartan (ARNI)
Volume Status	• Initial diuretic action of SGLT2 inhibitors
Kidney Function	• Initial small decline in eGFR with RAAS blockers, MRAs, and SGLT2 inhibitors • Longer term preservation of kidney function with neprilysin inhibitors and SGLT2 inhibitors
Serum K^+	• Neprilysin inhibition and SGLT2 inhibition do not increase K^+ and may reduce the risk of MRA-induced hyperkalemia • Remember sacubitril/valsartan (ARNI) includes an ARB

Personal communication, John McMurray, MD, FRCP, FESC, FACC, FAHA.

Scheme for Rapid Sequencing of HFrEF Medication

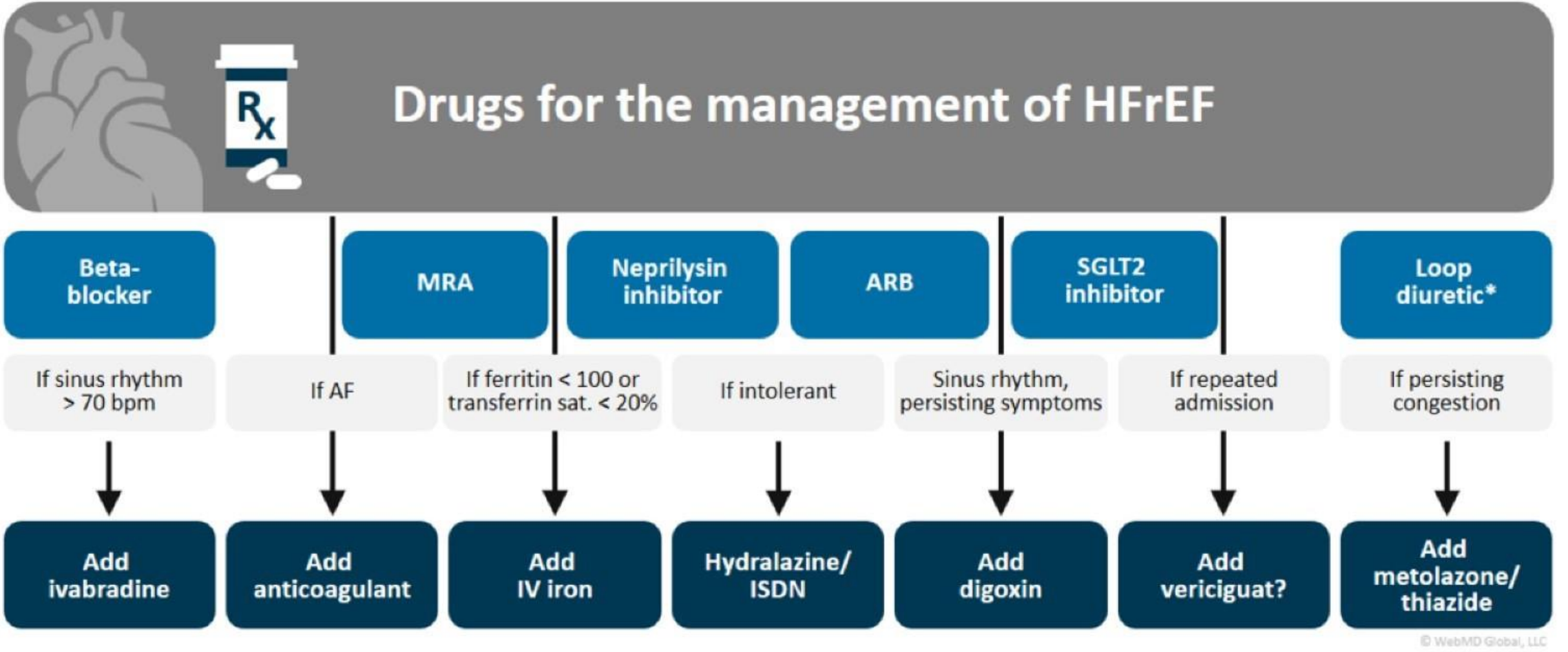


- The order of Step 2 and 3 may be reversed in a patient with a borderline SBP
- Patients already receiving an ACEI/ARB may be switched to ARNI and started on a MRA at the same time

SBP, systolic blood pressure.

Packer J, et al. Eur J Heart Fail. 2021;23:882-894.

Drug Sequencing



*In patients with congestion.

Mishra S, et al. *Indian Heart J.* 2018;70:105-127; Personal communication, John McMurray, MD, FRCP, FESC, FACC, FAHA.

Monitoring Patients With Drug Uptitration

- It is recommended that monitoring takes place in the hospital setting
- Monitor BP and signs and symptoms of HF and congestion
- Monitor eGFR and potassium levels
- For patients on BB therapy, it is also important to monitor HR

Advanced heart failure with worsening prognosis

- **> 1 admission or unplanned visit to HF clinic within 12 months**
- **Prior inotrope use**
- **Intolerant to beta blocker, RASi/ ARNI**
- **LV EF < 20**
- **Worsening RV function**
- **Worsening renal/liver function**
- **Ventricular arrhythmia, ICD shocks**
- **Need foe escalating diuretic doses for persistent congestion**
- **SBP < 90 and /or signs of peripheral hypo-perfusion**

Timing for referral for MCS & transplant

- **g**

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

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.

ESC
European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

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

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
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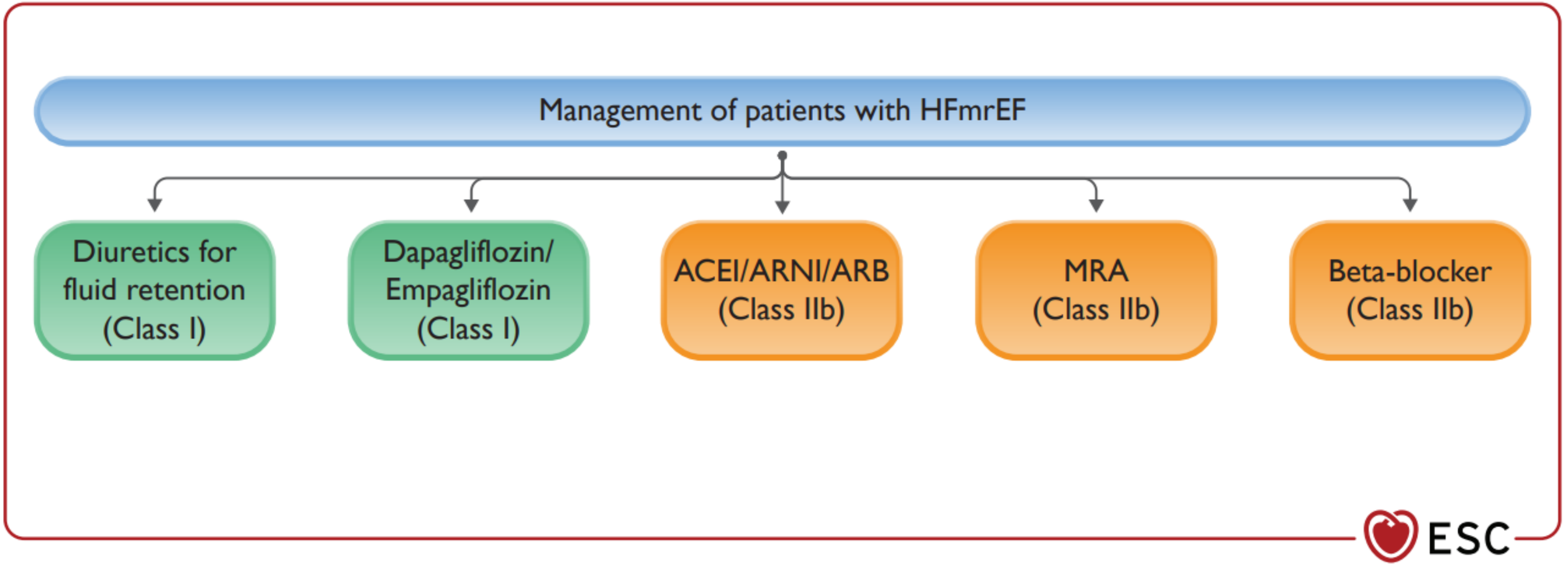


Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid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

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

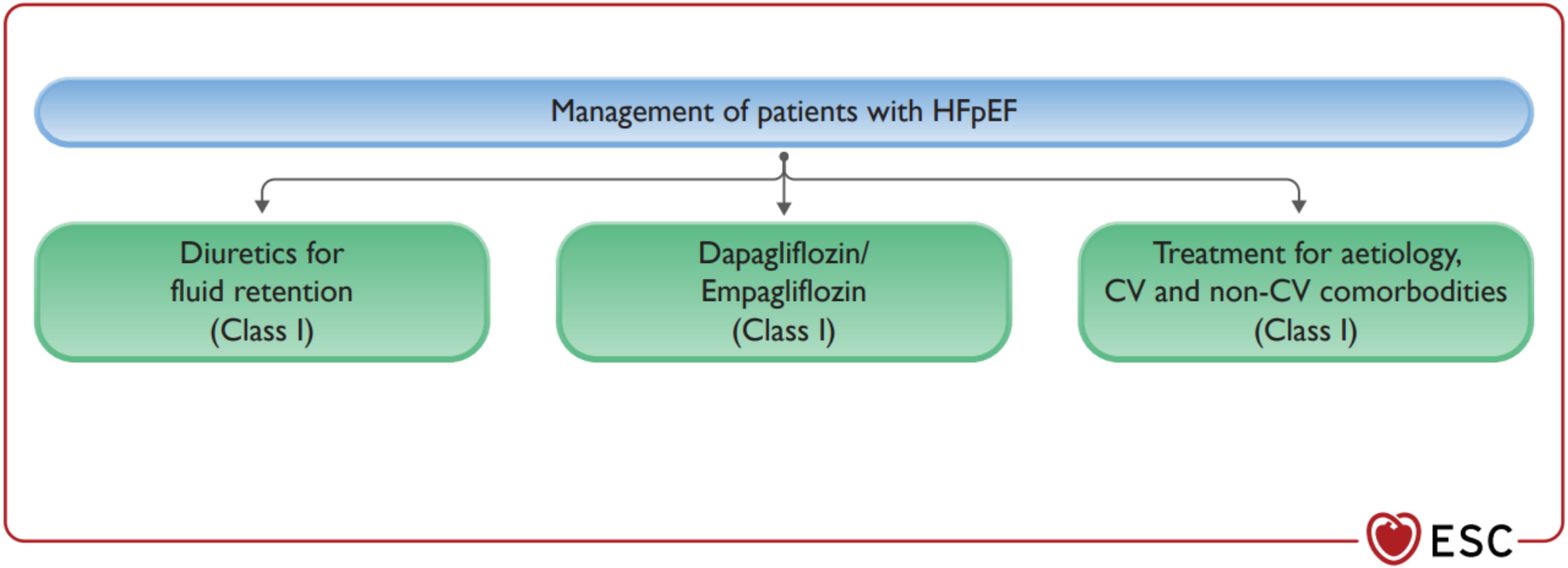


Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class	Level
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.	I	C

CV=cardiovascular; HF=heart failure; SGLT2=sodium-glucose co-transporter 2.

What's News (Summary)

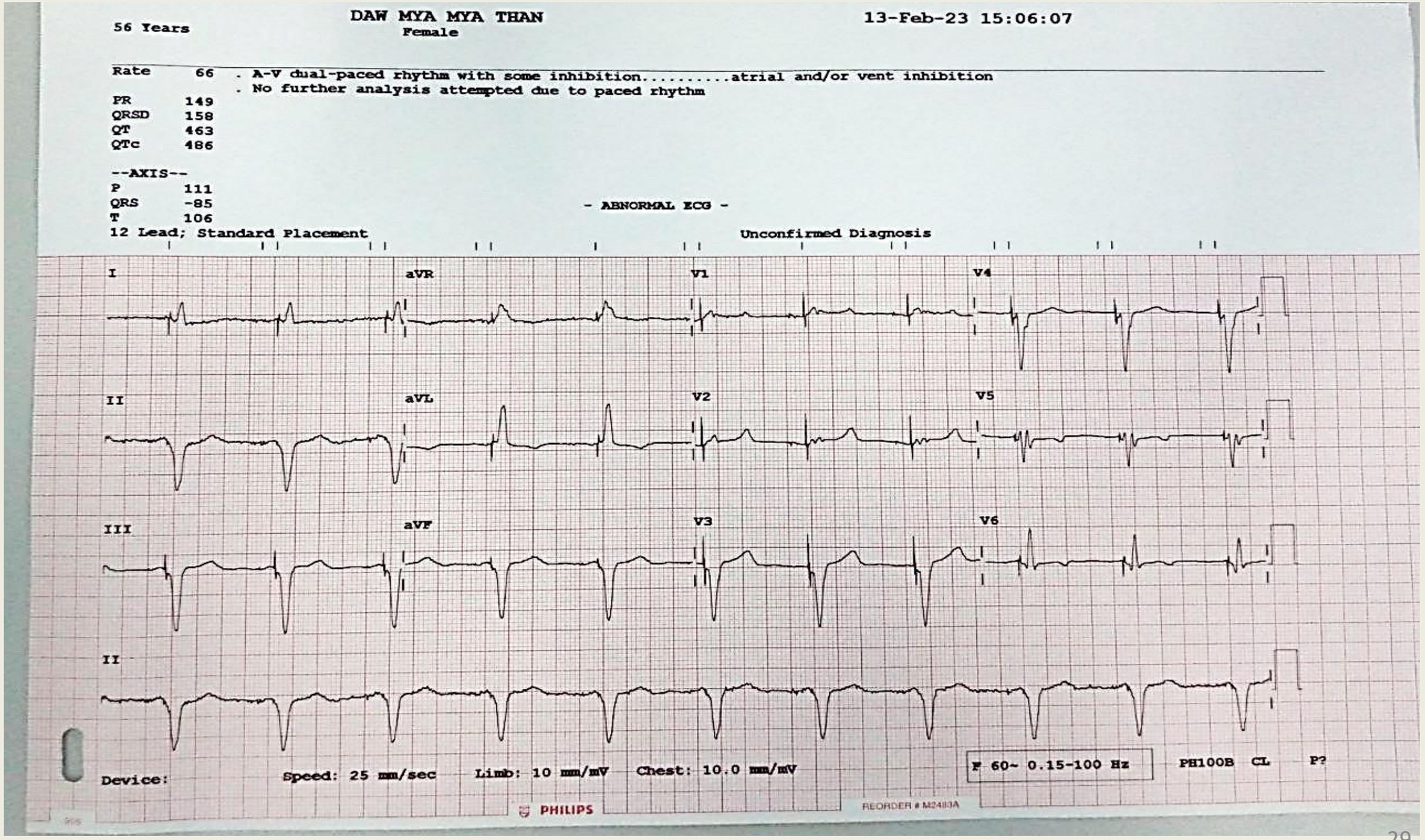
- **New classification of HF**
- **CMRI for suspected infiltrative CM, hemochromatosis, LV Non-compaction**
- **GDMT for HFrEF, 2 new medications: ARNI as a replacement for ACEI, SGLT2i (Dapagliflozin & Empagliflozin) as Class I recommendation to reduce HF hospitalization & CV death**
- **GDMT for HFmrEF & HFpEF, Diuretics & SGLT2i become Class I recommendation**
- **ICD recommendation for primary prevention of SCD: either ischemic (Class I) or non-ischemic (Class IIa), LVEF <35%, despite 3 months of GDMT with expected survival > 1 yr**
- **CRT recommendation for symptomatic HFrEF, EF <35%, LBBB > 150 ms or high grade AVB with need for pacing (Class I recommendation)**

What's News (Summary)

- For prevention of HF, appropriate Tx of HT, statin, SGLT2i in DM with high ASCVD risk, counseling against smoking, alcohol, drug use & obesity , class I recommendation
- For patients with AF, anticoagulation for CHA2DS2-VASc ≥1 in men, ≥2 in women (Class IIa), preferably DOAC unless mechanical prosthetic valve or moderate/ severe stenosis
- Beta blocker should be considered for short- or long - term rate control in HF with AF
- All HF patients periodically screened for Fe deficiency anemia and Fe supplement should be considered
- Influenza, pneumococcal & ? Covid vaccinations should be considered to prevent HF hospitalization (Class II a)

Case Scenario

- **56 yr, lady with Non-ischemic DCM (CHF) since 2011**
- **LBBB with LV EF 30% in 2011**
- **Pharmacological Rx & Cardiac re-synchronization (CRT-D) in 2012**
- **No more admission for HF since 2012**
- **CRT-D generator was changed in 2019**
- **Current medications: Frusemide 20 mg alternate day, Spironolactone 25 mg OD, Uperio (ARNI) 50 mg BD, Corolan (Ivabradine) 5 mg BD, Atorvastatn 10 mg OD,**
- **Carvedilol 3.125 mg BD, Empagliflozin 10 mg OD**


56 Years
DAW MYA MYA THAN
Female
13-Feb-23 15:06:07
Rate 66
PR 149
QRSD 158
QT 463
QTc 486
. A-V dual-paced rhythm with some inhibition.....atrial and/or vent inhibition
. No further analysis attempted due to paced rhythm
--AXIS--
P 111
QRS -85
T 106
- ABNORMAL ECG -
12 Lead; Standard Placement
Unconfirmed Diagnosis
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Device:
Speed: 25 mm/sec
Limb: 10 mm/mV
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PH100B CL
P?
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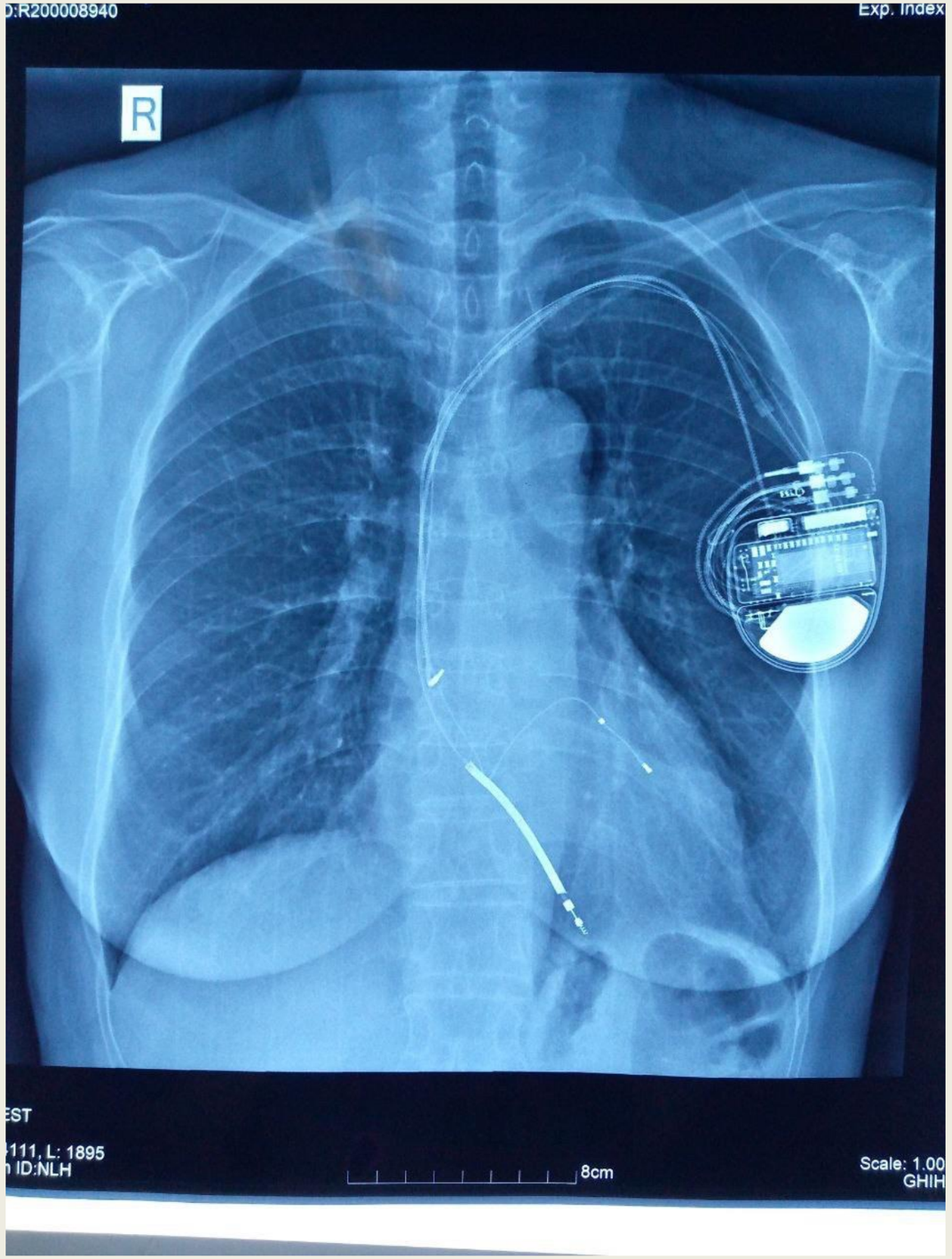
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8cm
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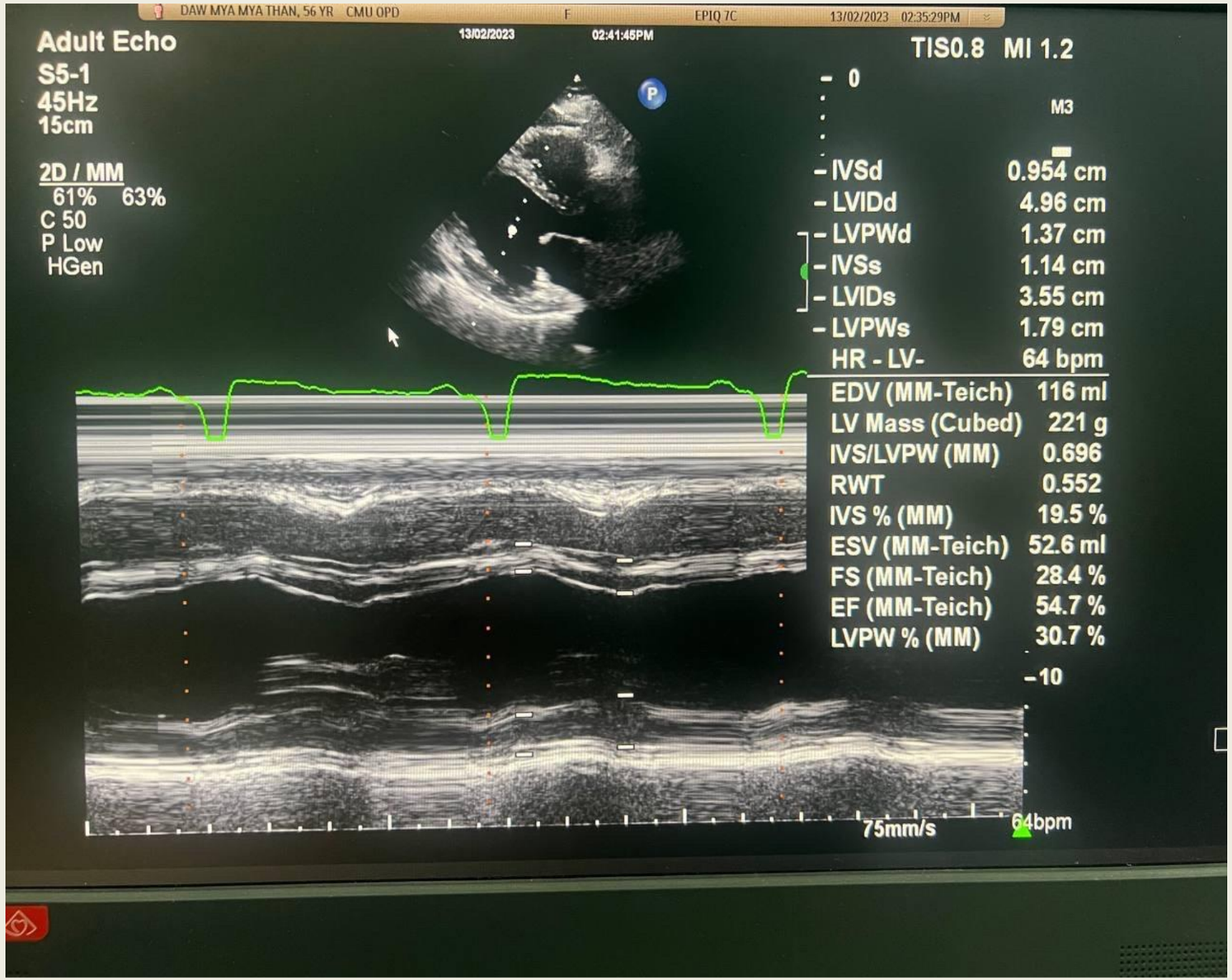
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F
EPIQ 7C
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Adult Echo
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45Hz
15cm
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TIS0.8 MI 1.2
2D / MM
61% 63%
C 50
P Low
HGen
M3
IVSd 0.954 cm
LVIDd 4.96 cm
LVPWd 1.37 cm
IVSs 1.14 cm
LVIDs 3.55 cm
LVPWs 1.79 cm
HR - LV- 64 bpm
EDV (MM-Teich) 116 ml
LV Mass (Cubed) 221 g
IVS/LVPW (MM) 0.696
RWT 0.552
IVS % (MM) 19.5 %
ESV (MM-Teich) 52.6 ml
FS (MM-Teich) 28.4 %
EF (MM-Teich) 54.7 %
LVPW % (MM) 30.7 %
75mm/s
64bpm

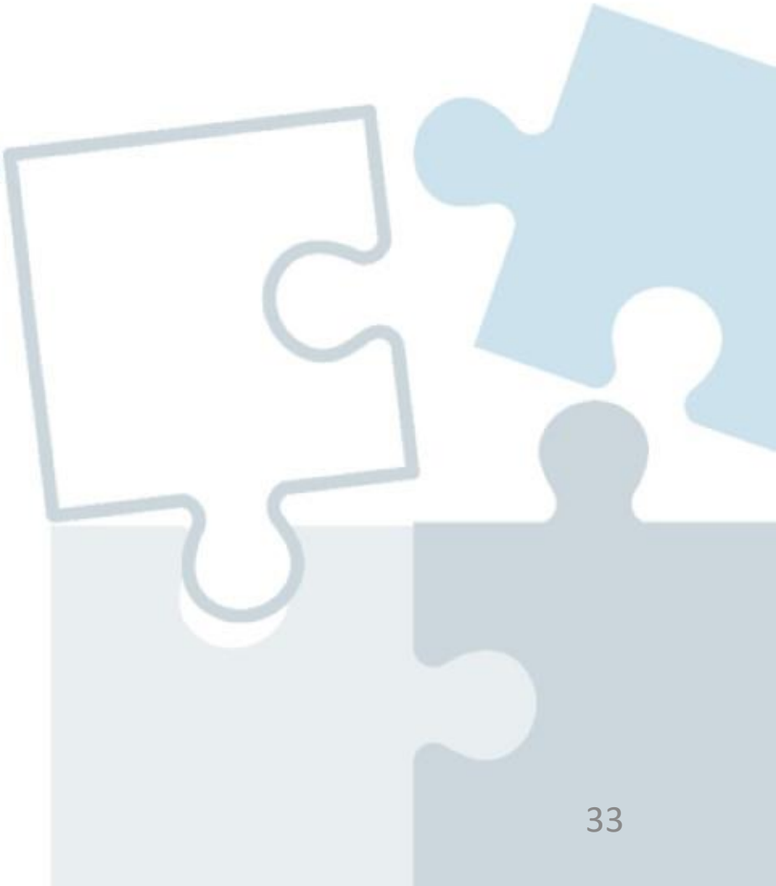
Conclusion

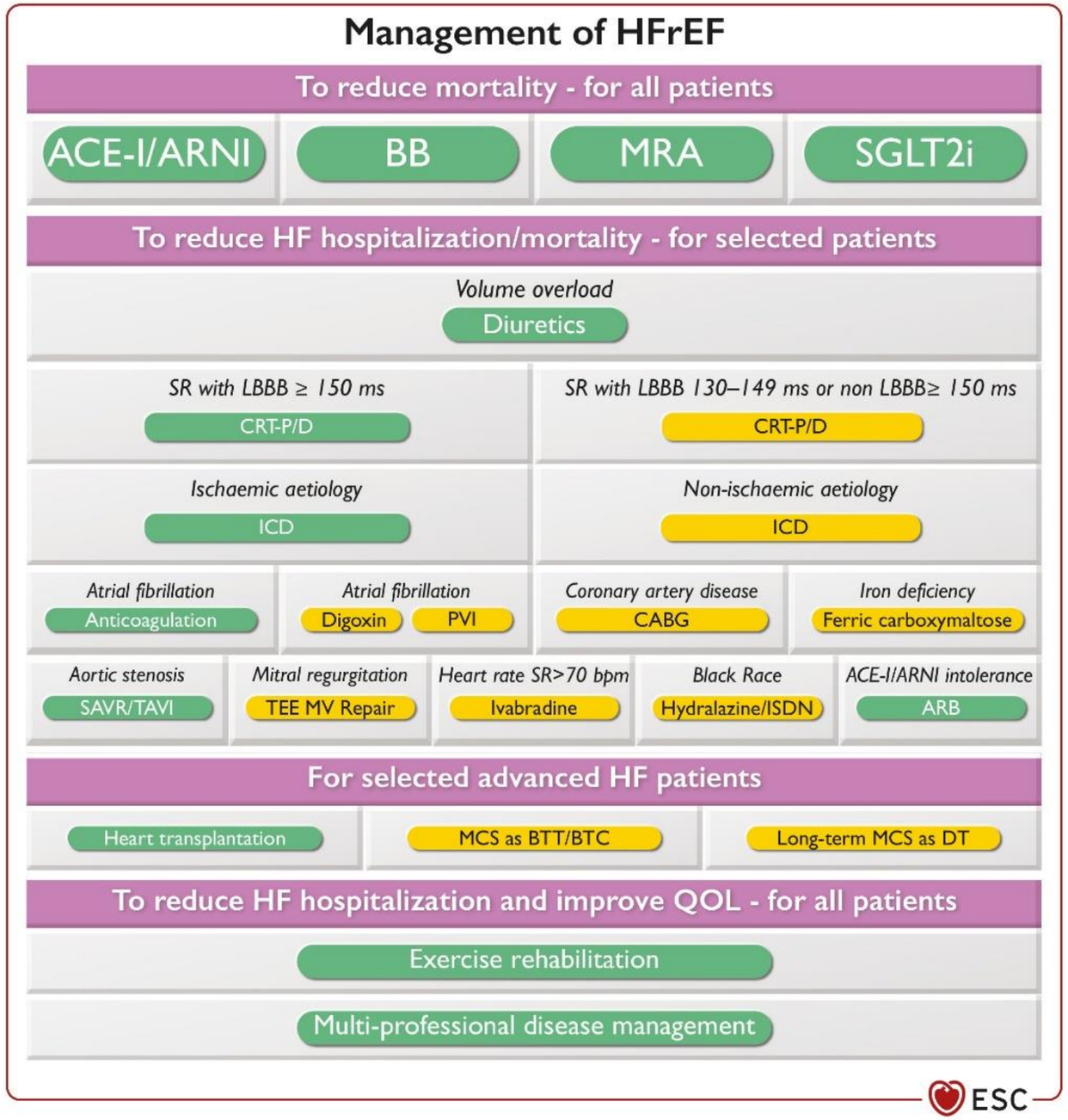
- **CHF is highly prevalent condition & also associated with high rates of morbidity & mortality, and poses a significant strain on the healthcare system**
- **A paradigm shift in heart failure management in recent years and various international guidelines have been highlighting the newer medications and innovations to bring down the heart failure hospitalization, morbidity and mortality**
- **GDMT encompasses clinical evaluation, diagnostic testing and both pharmacological and procedural treatments**
- **New evidence-based guidelines regarding the treatment of HF help to support clinicians in practice**
- **Robust evidence of clinical trials are approving the cardiovascular protection benefits such as ARNI, SGLT2 inhibitors & Ivabradine in HF updating the standard care in the Mx of HF**

THANK YOU

Summary and Conclusion

- The new universal definition of HF adds precision to the diagnosis of HF
- LVEF is a dynamic measure and can change over time
- New evidence-based guidelines regarding the treatment of HF are available to help support clinicians in practice
- Robust clinical trial evidence is now available regarding the benefit of SGLT2 inhibition in the management of patients with HFpEF





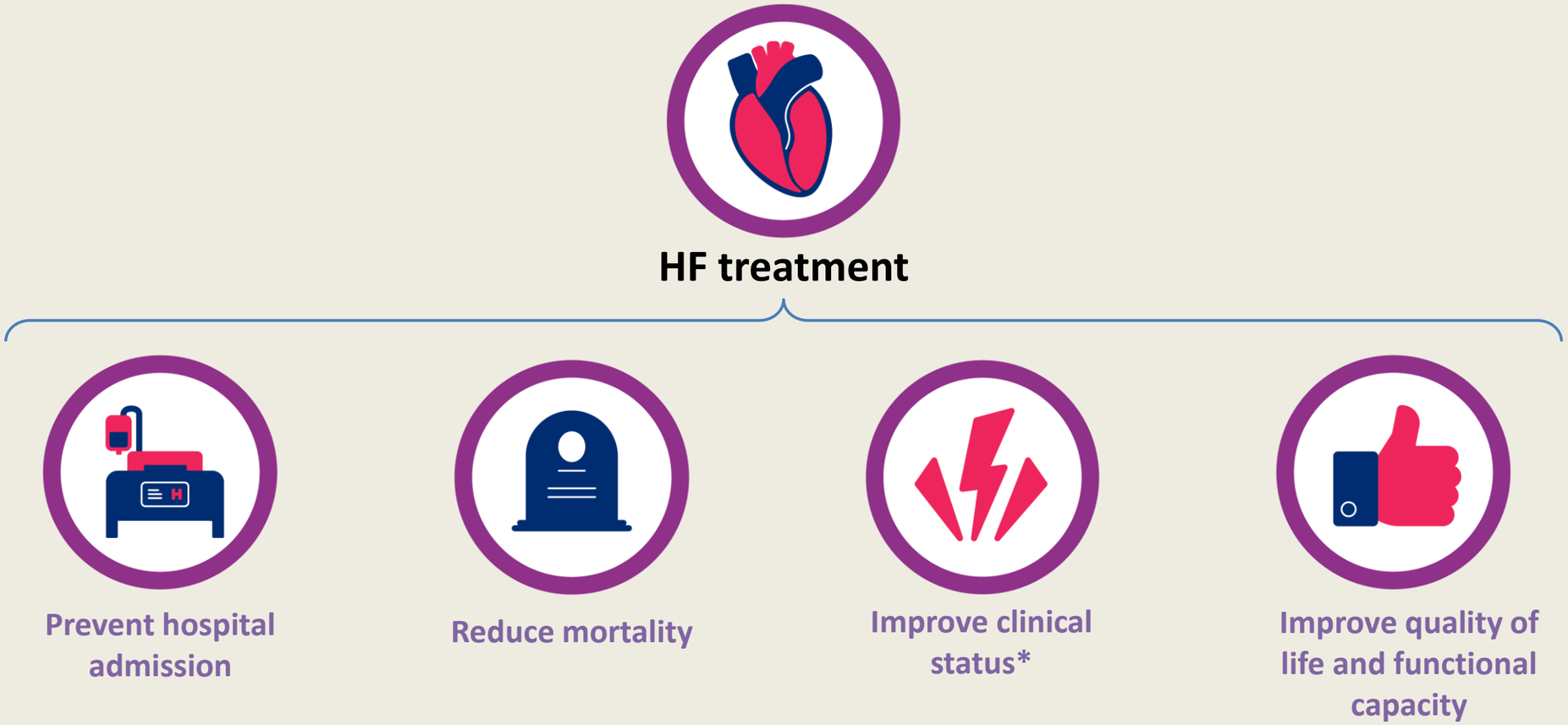
Strategic phenotypic overview of the management of heart failure with reduced ejection fraction

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; b.p.m. = beats per minute; BTC = bridge to candidacy; BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see Table 1 for further details on classes of recommendation).
The Figure showsmanagement options with Class I and IIa recommendations. See the specific Tables for those with Class IIb recommendations.

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)

Treatment of patients with Heart Failure has multiple goals[1,2]



*Clinical status includes (but is not limited to) heart rate, heart rhythm, respiratory rate, oxygen saturation, blood pressure, weight, fluid balance, HF symptoms and renal function[1]

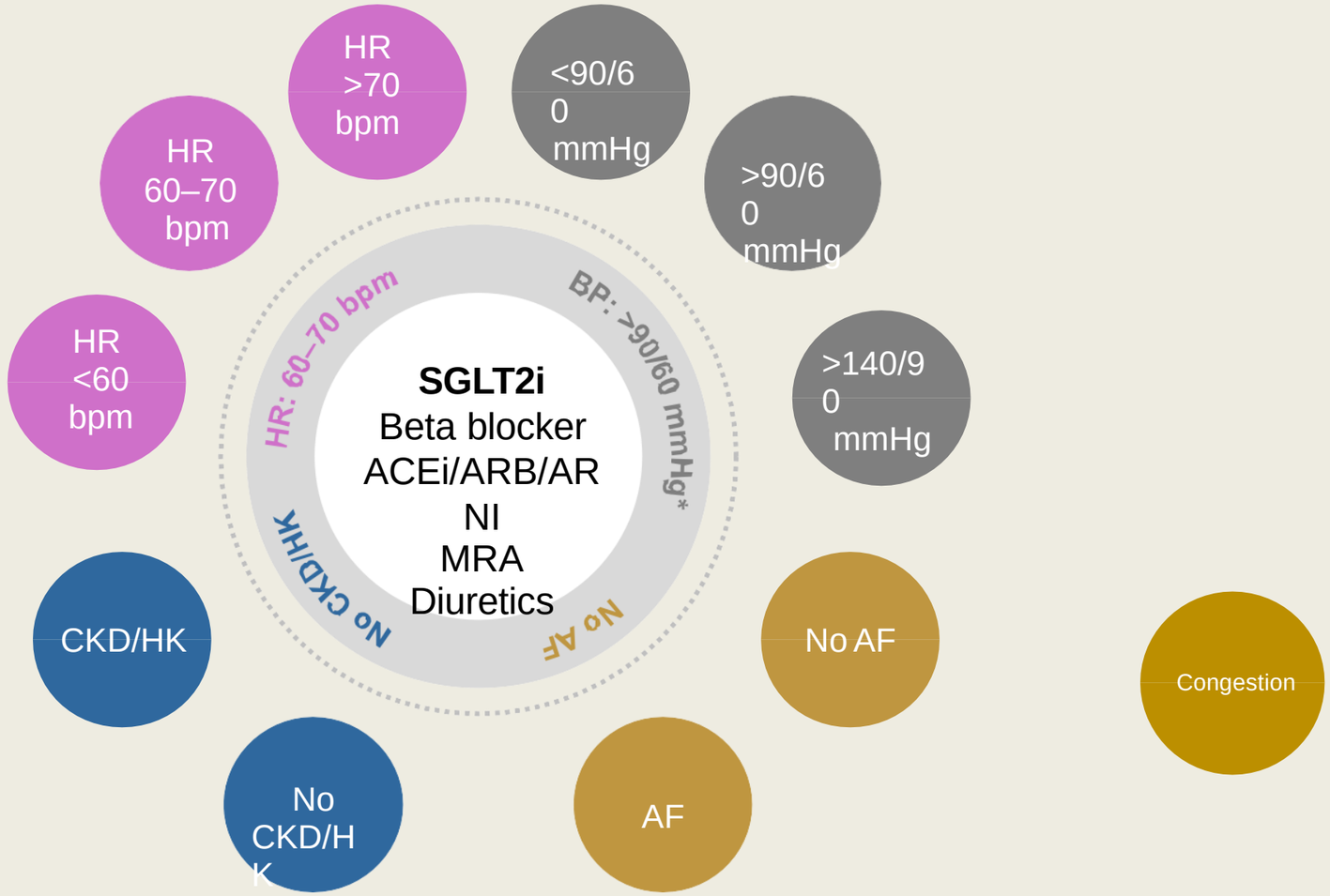
The HFA-ESC consensus document highlights key characteristics that should be considered in the management of HFrEF

ESC European Society of Cardiology
European Journal of Heart Failure (2021) 23, 872–881
doi:10.1002/ejhf.2206
POSITION PAPER

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

1. Clinical profile
2. Co-morbidities
3. Baseline cardiovascular risk

The HFA-ESC consensus document recommends **maintaining SGLT2i** across all phenotypes listed



*In patients with predominant chronic coronary syndrome, blood pressure threshold is 120/80 mmHg. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; HFA- ESC, Heart Failure Association of the European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co- transporter-2 inhibitor.

Rosano GMC *et al. Eur J Heart Fail*. 2021;23:872.

Recommendations for SGLT2 inhibitors in HF: Overview

Only the AHA/ACC/HFSA Guidelines were published AFTER disclosure of the EMPEROR-Preserved trial

HFrEF (LVEF ≤40%)	HFmrEF (LVEF 41–49%)	HFpEF (LVEF ≥50%)
2021 CCS/CHFS Guidelines[1]	2022 AHA/ACC/HFSA Guidelines[3]	
2021 ESC Guidelines[2]		
2022 AHA/ACC/HFSA Guidelines[3]		

- All include **SGLT2 inhibitors as first-line therapy** for HFrEF, creating a **four foundational pillars treatment strategy**

HFmrEF

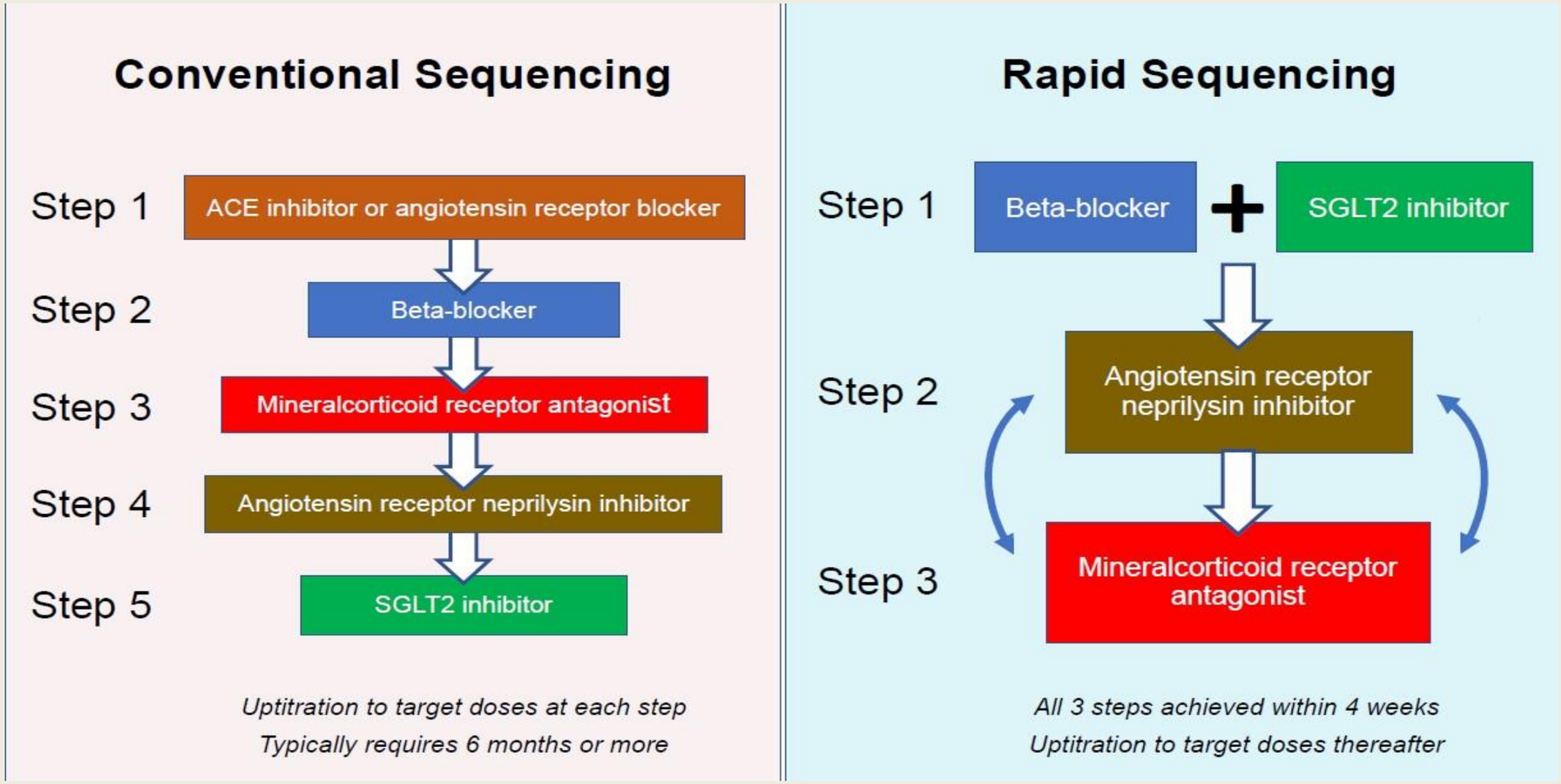
- **SGLT2 inhibitors** have a **Class 2a recommendation** in HFmrEF
- **Weaker recommendations** (Class 2b) are made for ARNI, ACEi, ARB, MRA and BB in HFmrEF

HFpEF

- **SGLT2 inhibitors** have a **Class 2a recommendation** in HFpEF
- **Weaker recommendations** (Class 2b) are made for ARNI, ARB and MRA in HFpEF

1. McDonald M *et al. Can J Cardiol.* 2021;37:531; 2. McDonagh TA *et al. Eur Heart J.* 2021;42:3599; 3. Heidenreich PA *et al. J Am Coll Cardiol.* 2022; doi:10.1016/j.jacc.2021.12.012.

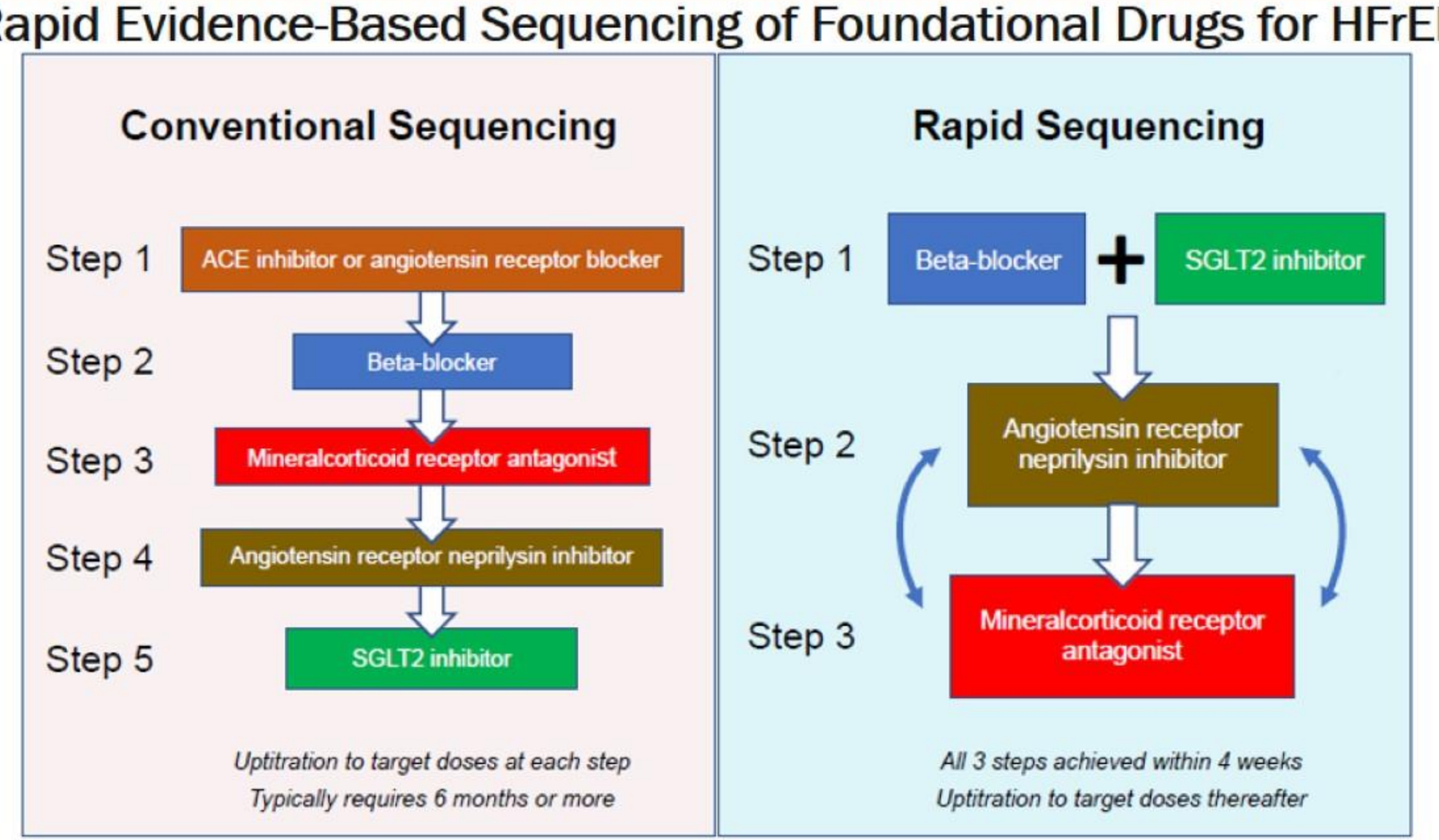
Novel Sequencing Strategies – Dual Start



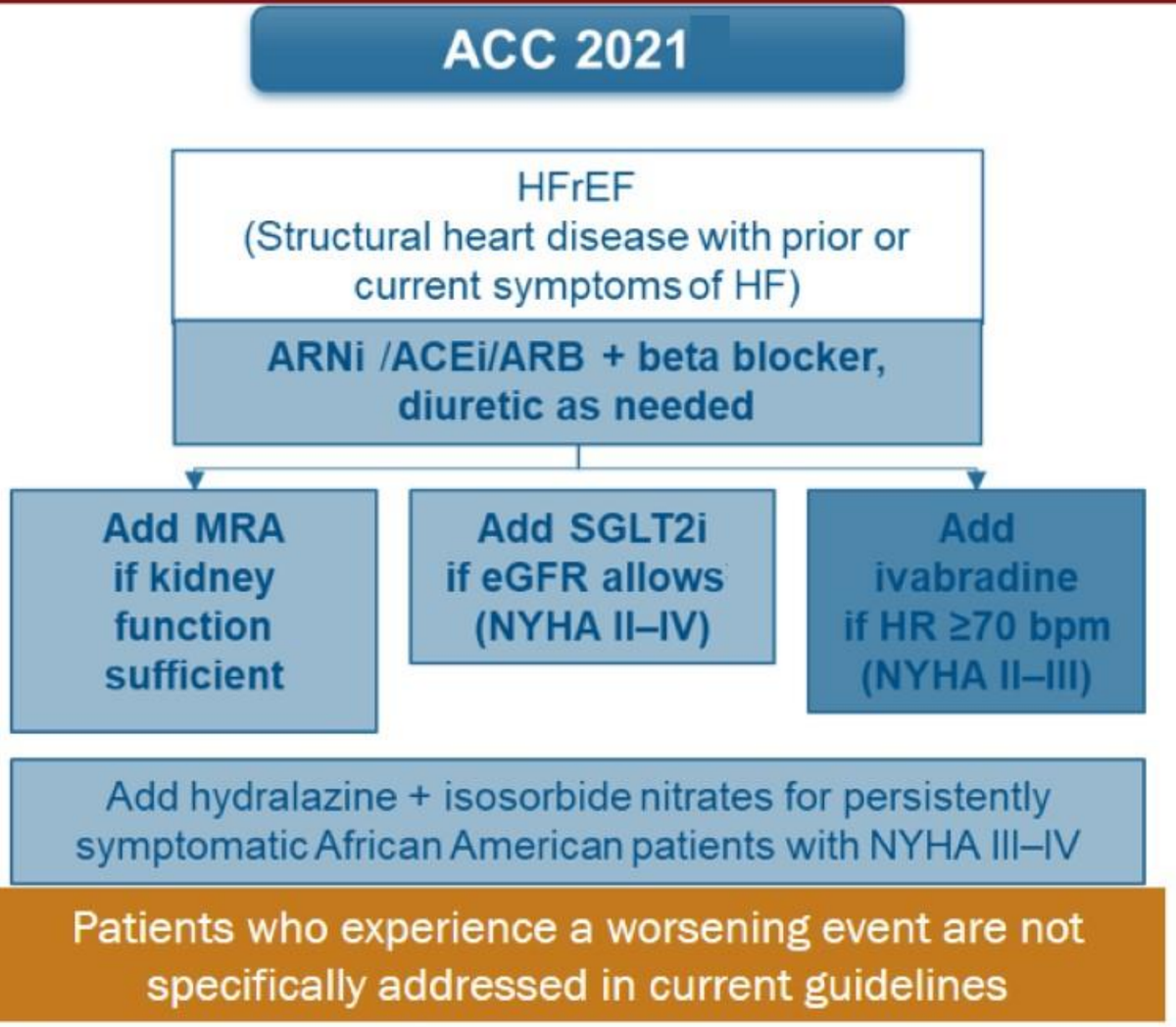
Eur J Heart Fail. 2021 Mar 11. doi: 10.1002/ejhf.2149

Consensus

Focus is On 4 Foundational Drugs and Add Drugs Rapidly



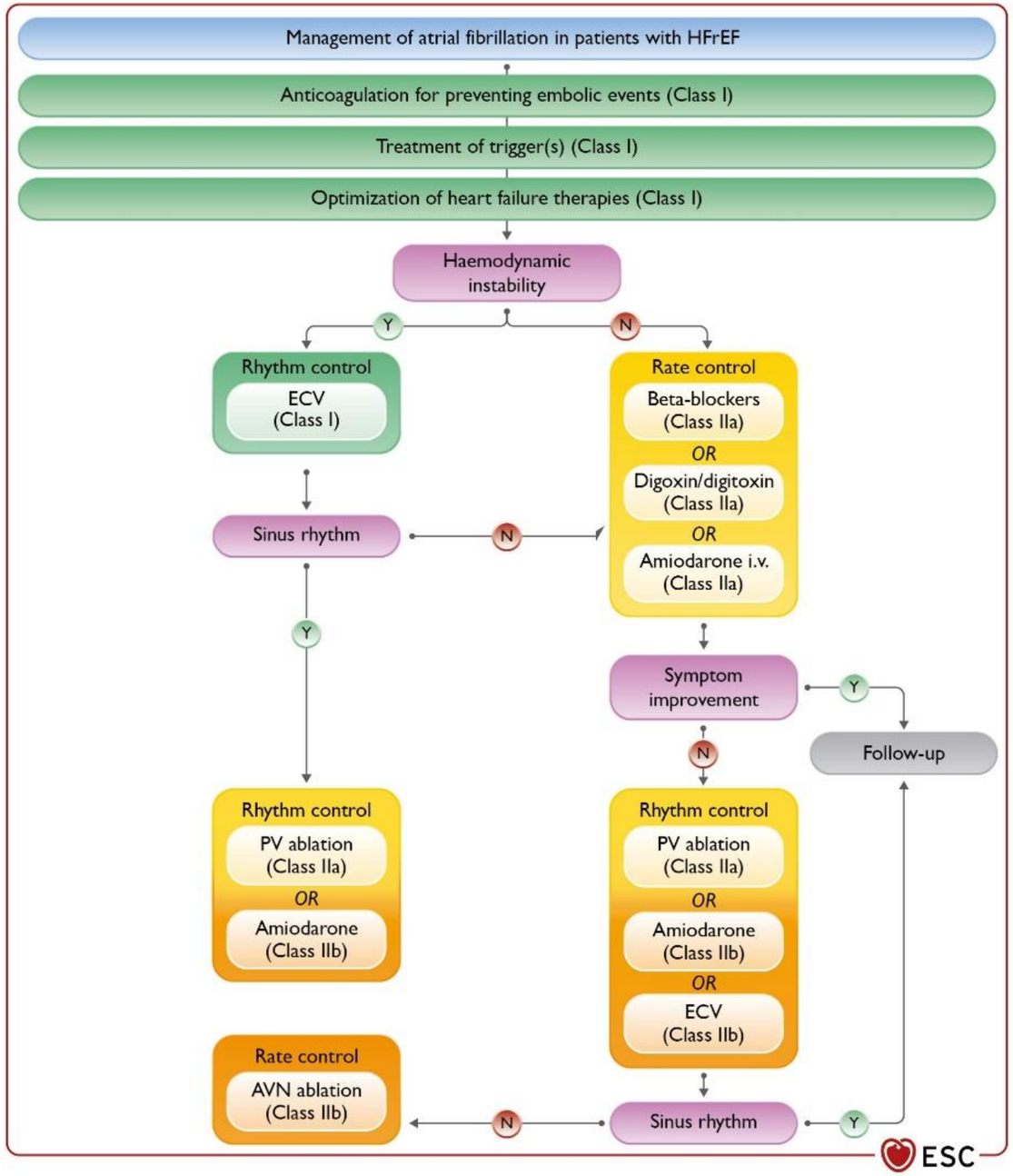
2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment



ACC, American College of Cardiology.

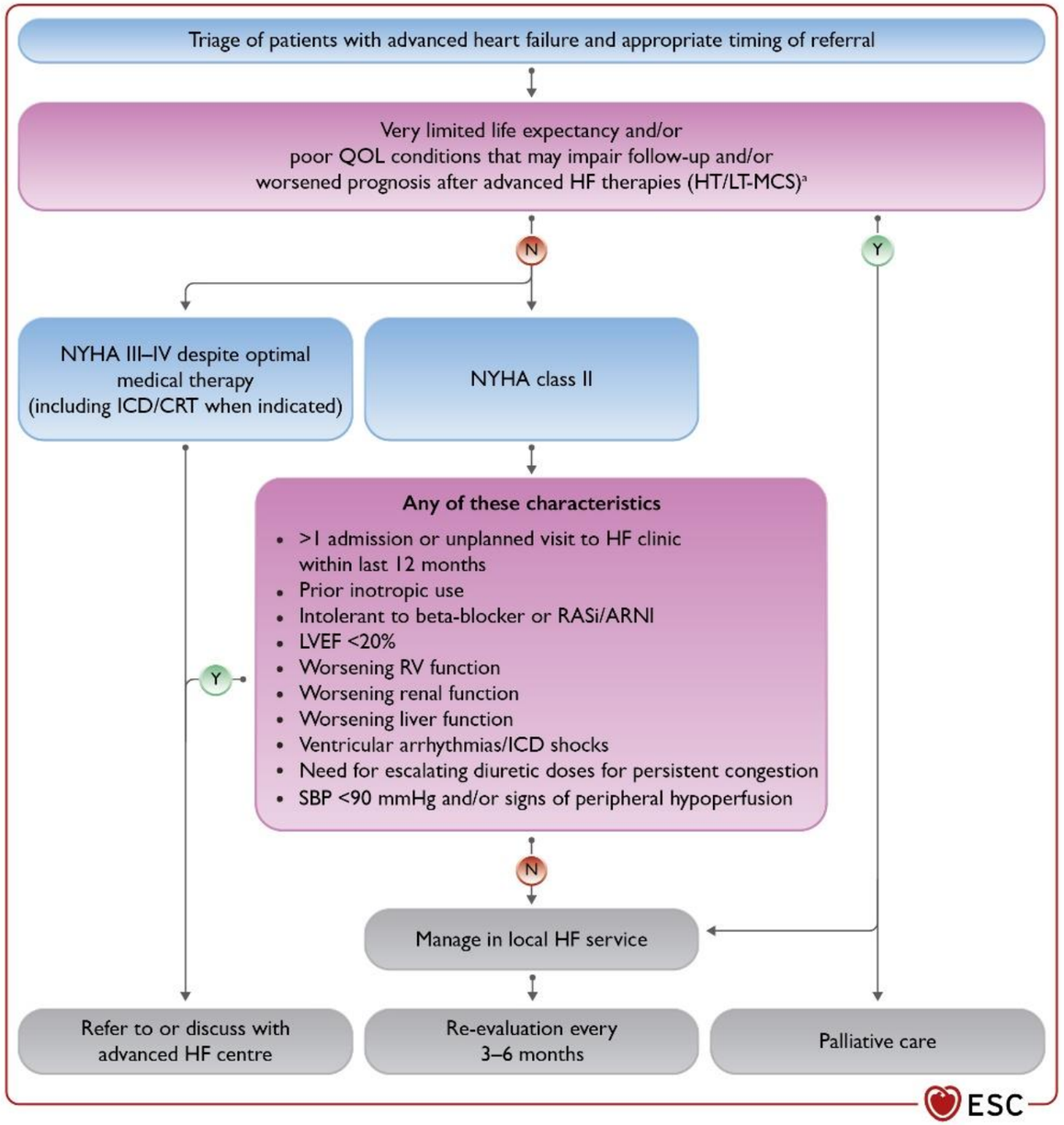
Reprinted from Writing Committee, Maddox TM, Januzzi JL Jr, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb 16;77(6):772-810, Page 779, Copyright 2021, with permission from Elsevier.

Management of atrial fibrillation in patients with heart failure



AF = atrial fibrillation; AVN = atrioventricular node; ECV = electrical cardioversion; HF = heart failure; i.v. = intravenous; PV = pulmonary vein.
Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa; Orange for Class of recommendation IIb; Red for Class of recommendation III (see Table 1 for further details on classes of recommendation).

www.escardio.org/guidelines



Triage of patients with advanced heart failure and appropriate timing of referral

ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; HF=heart failure; HT = heart transplantation; ICD=implantable cardioverter-defibrillator; LT-MCS = long-term mechanical circulatory support; LVEF=left ventricular ejection fraction; NYHA = New York Heart Association; RASi = renin-angiotensin system inhibitor; RV = right ventricular; SBP = systolic blood pressure; QOL = quality of life.

[a]Limited life expectancy may be due by major comorbidities such as cancer, dementia, end-stage organ dysfunction; other conditions that may impair follow-up or worsen post-treatment prognosis include frailty, irreversible cognitive dysfunction, psychiatric disorder, or psychosocial issues.