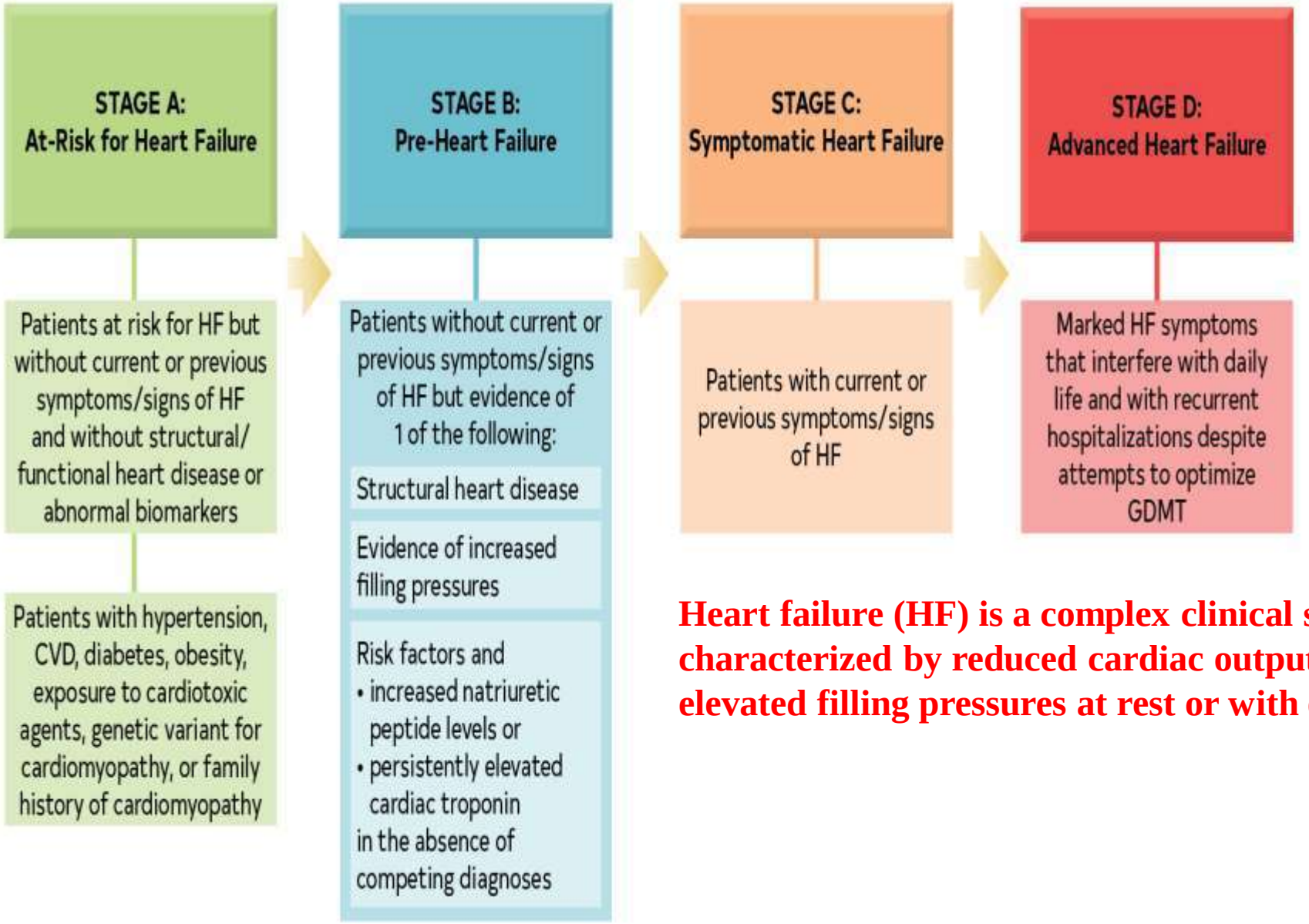
Heart failure with mildly reduced ejection fraction
The middle child of heart failure

Dr M Sudhakar Rao

MD DM FACC FESC FSCAI



AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

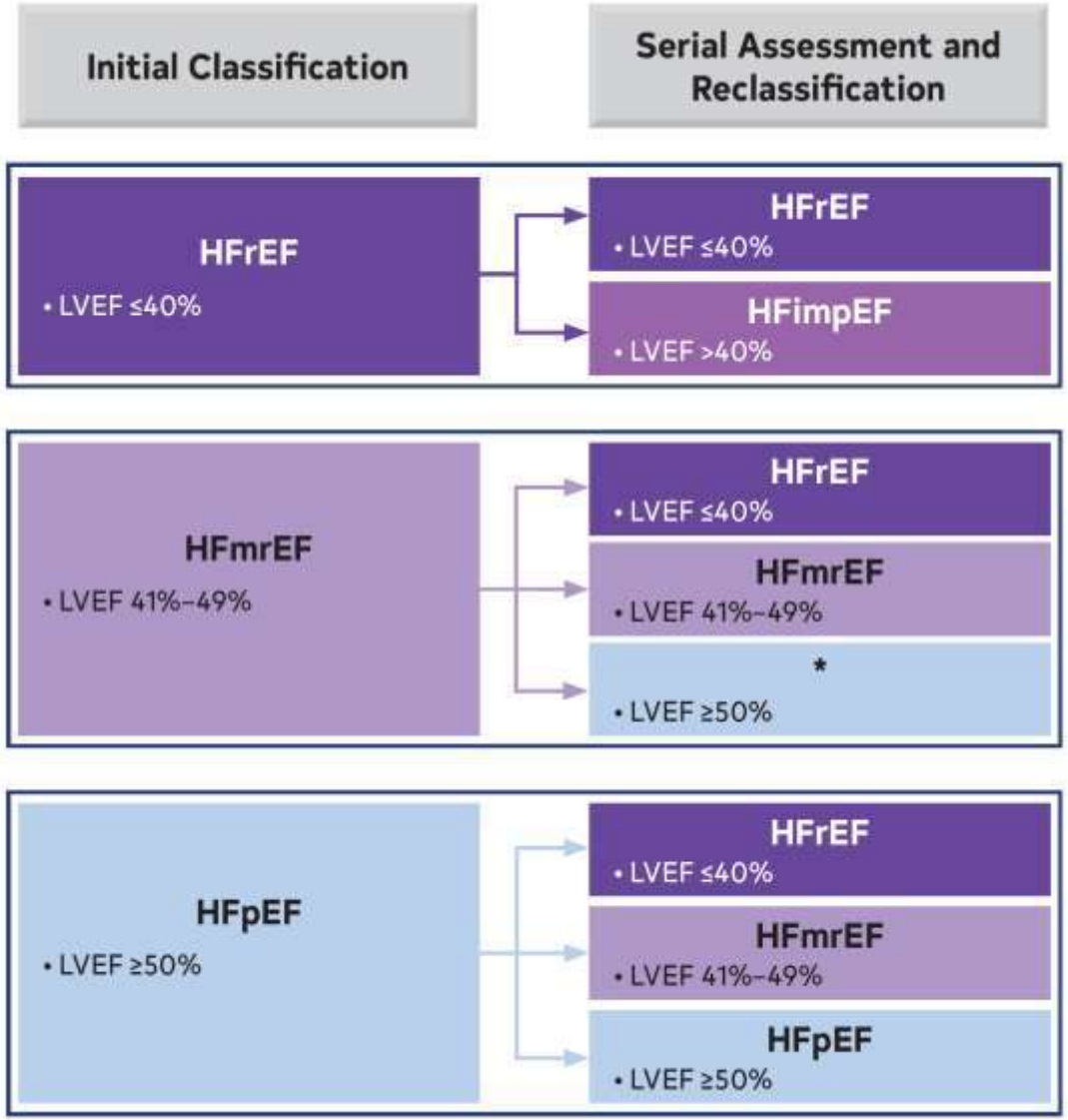
Heart failure (HF) is a complex clinical syndrome characterized by reduced cardiac output and/or elevated filling pressures at rest or with exertion.

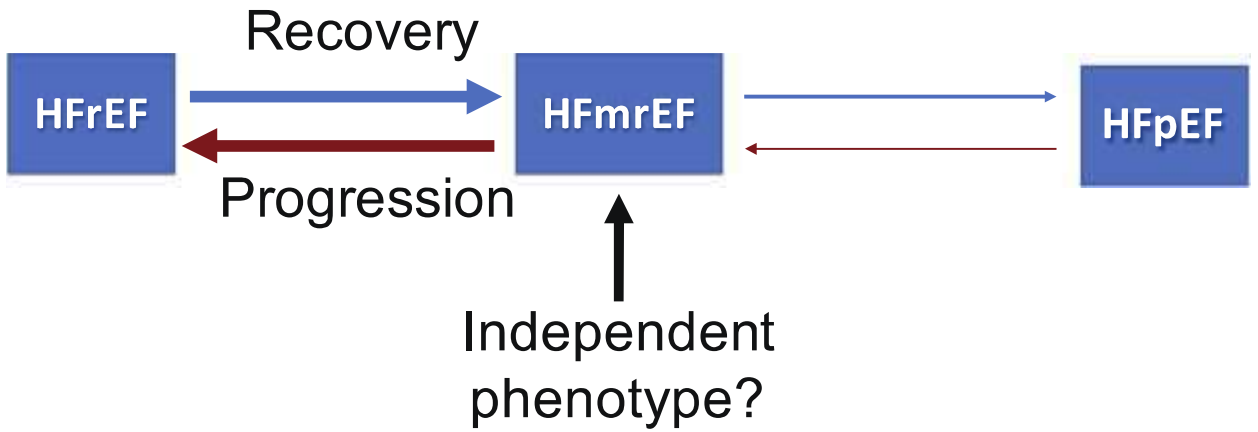
Classification of HF by LVEF

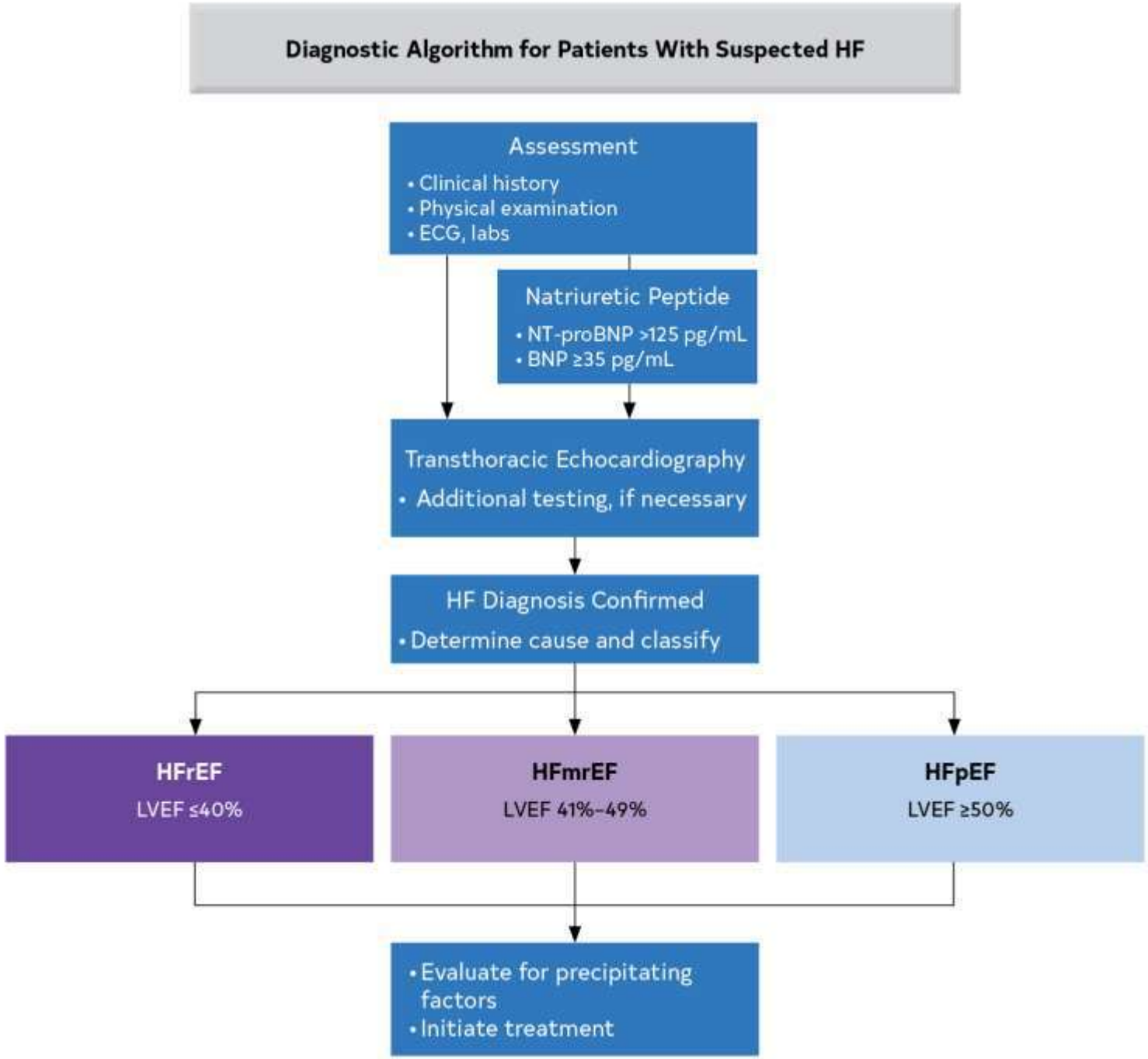
Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	• LVEF ≤40%
HFimpEF (HF with improved EF)	• Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	• LVEF 41%–49% • Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	• LVEF ≥50% • Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

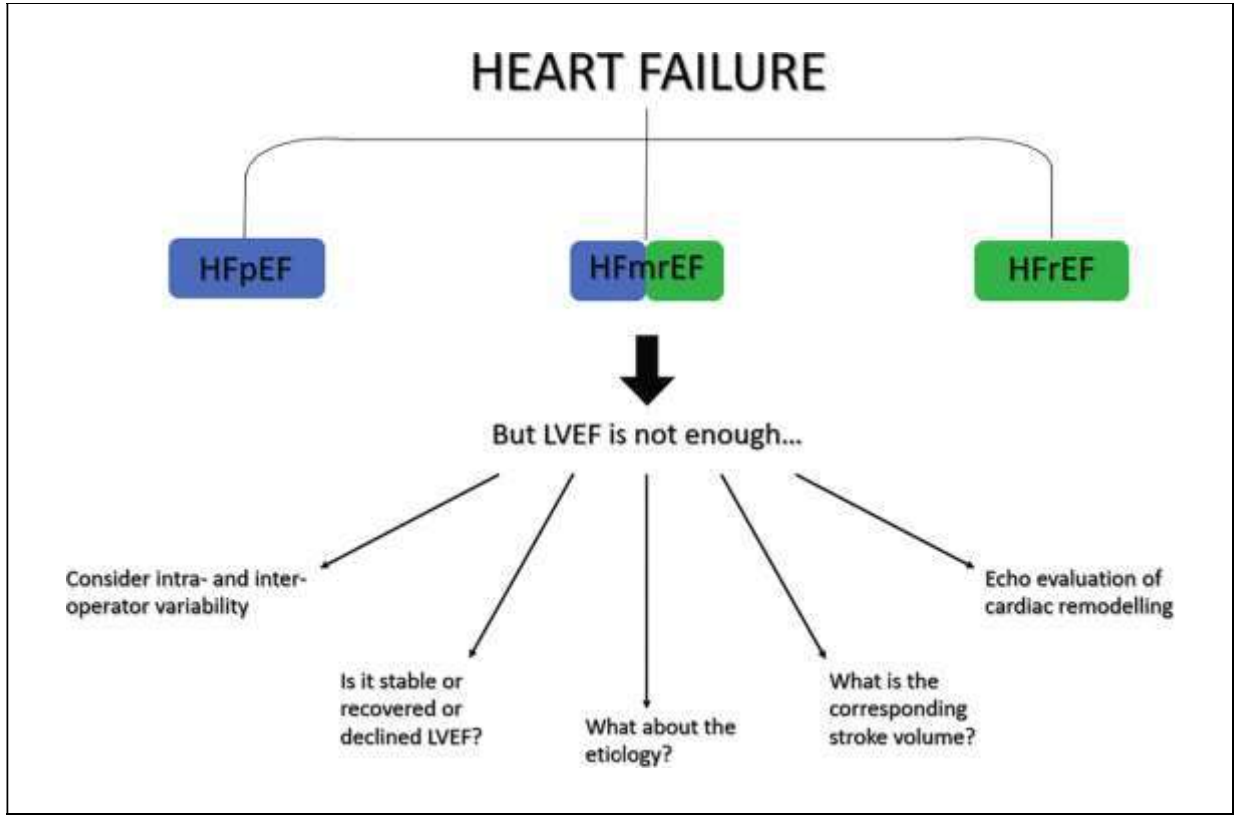
Classification and Trajectories of HF Based on LVEF






Diagnostic Algorithm for Patients With Suspected HF
Assessment
• Clinical history
• Physical examination
• ECG, labs
Natriuretic Peptide
• NT-proBNP >125 pg/mL
• BNP ≥35 pg/mL
Transthoracic Echocardiography
• Additional testing, if necessary
HF Diagnosis Confirmed
• Determine cause and classify
HFrEF
LVEF ≤40%
HFmrEF
LVEF 41%–49%
HFpEF
LVEF ≥50%
• Evaluate for precipitating factors
• Initiate treatment

Pros	Cons
Standardize the clinical approach Standardize the care The LVEF is a simple criterion to plan and design randomized trials Acknowledgement of a subgroup with a specific bio-clinical profile that is different from HFrEF and HFpEF Lack of other classifiers and targets that are reproducible and/or treatable	Large mobility of patient with HF between LVEF categories Lack of consideration of the underlying HF aetiology Poor information about the ventricular remodelling and/or ventricular dyssynchrony Intra-variability and inter-variability of the echo LVEF measurement Intrinsic limitations of LVEF alone HFmrEF patient cohort is a heterogeneous population with many phenotypes Loss of prognostic power of LVEF proportionally to the increase of LVEF values



Common Factors Precipitating HF Hospitalization With Acute Decompensated HF

ACS
Uncontrolled hypertension
AF and other arrhythmias
Additional cardiac disease (e.g., endocarditis)
Acute infections (e.g., pneumonia, urinary tract)
Nonadherence with medication regimen or dietary intake
Anemia
Hyper- or hypothyroidism
Medications that increase sodium retention (e.g., NSAID)
Medications with negative inotropic effect (e.g., verapamil)

ACS indicates acute coronary syndrome; AF, atrial fibrillation; and NSAID, nonsteroidal anti-inflammatory drug.

Other Potential Nonischemic Causes of HF

Cause	
Chemotherapy and other cardiotoxic medications	
Rheumatologic or autoimmune	
Endocrine or metabolic (thyroid, acromegaly, pheochromocytoma, diabetes, obesity)	
Familial cardiomyopathy or inherited and genetic heart disease	
Heart rhythm–related (e.g., tachycardia-mediated, PVCs, RV pacing)	
Hypertension	
Infiltrative cardiac disease (e.g., amyloid, sarcoid, hemochromatosis)	
Myocarditis (infectious, toxin or medication, immunological, hypersensitivity)	
Peripartum cardiomyopathy	
Stress cardiomyopathy (Takotsubo)	
Substance abuse (e.g., alcohol, cocaine, methamphetamine)	

HF indicates heart failure; PVC, premature ventricular contraction; and RV, right ventricular.

HFmrEF

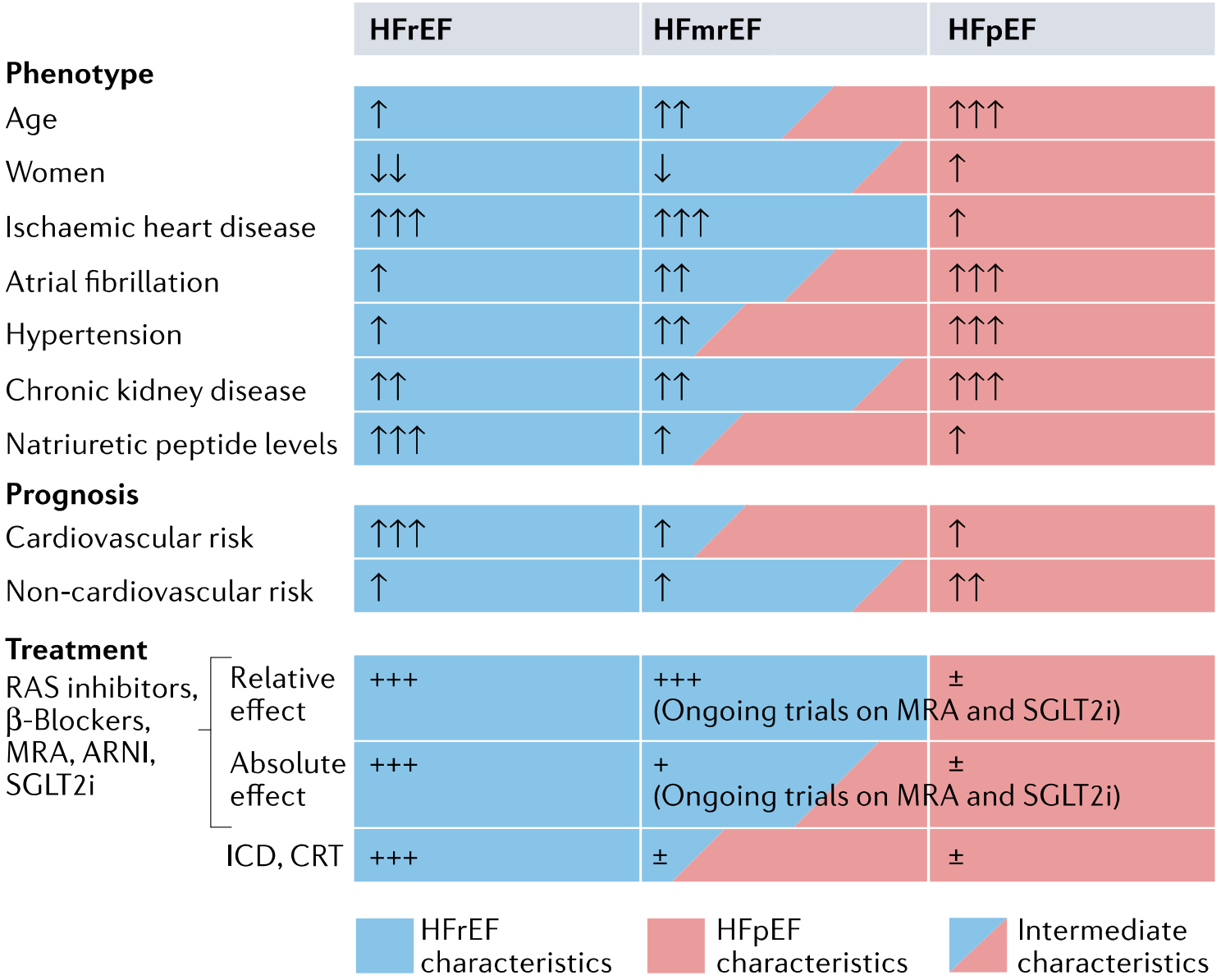
- ESC 2016 guidelines(mid –range EF)
- explore the “underlying characteristics, pathophysiology and treatment of this group of patients”
- Name changed in ESC 2021 guidelines(mildly-reduced)
- Evidence comes from CHARM-PRESERVED , TOPCAT, I-PRESERVE and PARAGON HF
- the presence of symptoms and/or signs of HF (i.e. elevated BNP or NT-proBNP and other evidence of structural heart disease) are **not considered mandatory anymore** for the diagnosis of HFmrEF if the measurement of EF is considered reliable

Epidemiology

- 10-25 %
- HFmrEF was 6.7 cases per 10,000 person- years, vs 26.9 and 34.9 in HFpEF and HFrEF, respectively(community based longitudinal study)
- 24% in the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) Registry and 21% in the Swedish HF (SwedeHF) Registry
- In the CHARM population, 17% had HFmrEF

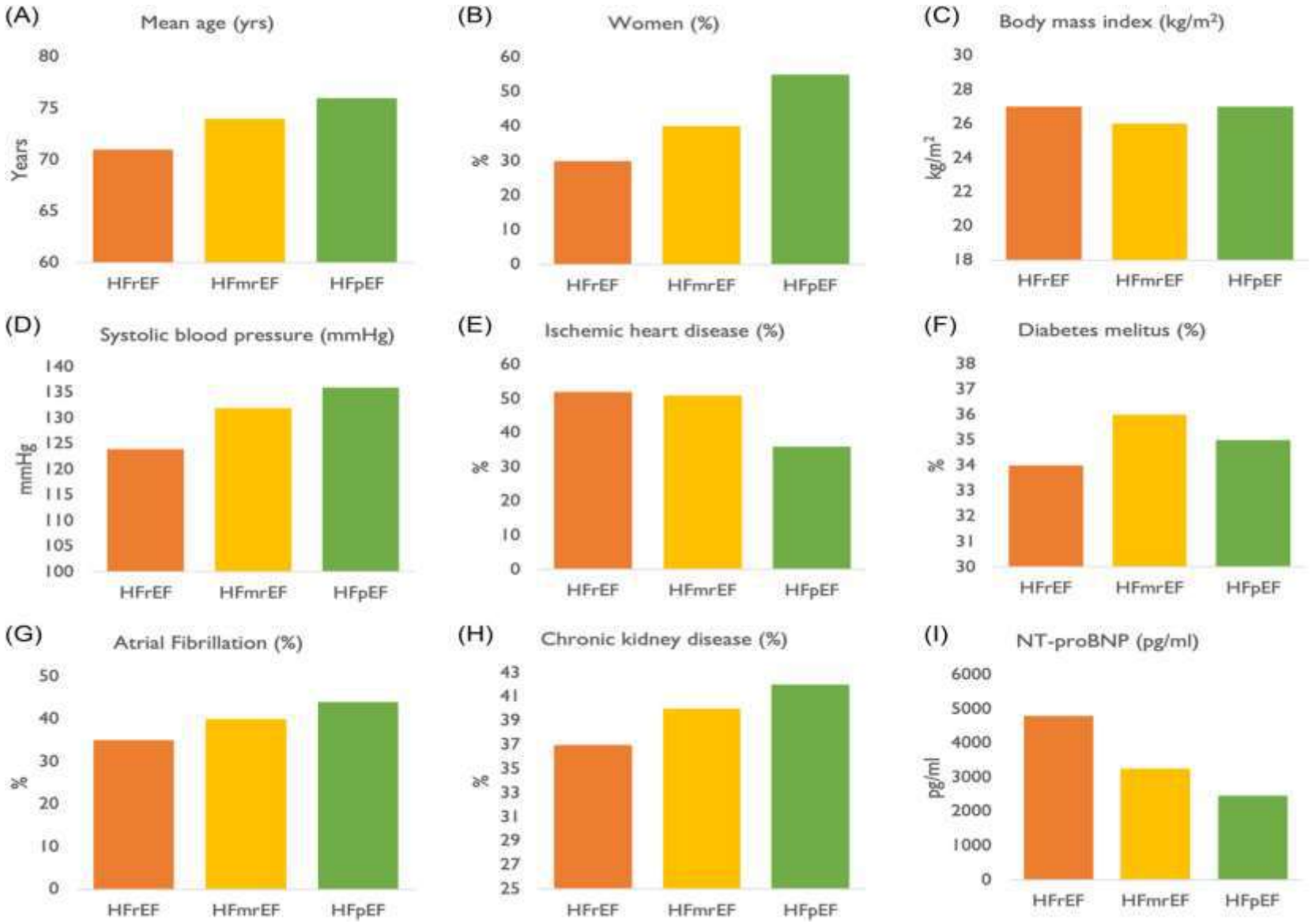
Clinical characteristics of HFmrEF

- OPTIMIZE-HF, ADHERE registry and ESC HF LT
- Ischemic etiology , AF, DM , COPD
- ESC HF LT – younger age , male sex, ischemic etiology and lower prevalence of AF
- Less symptomatic , less likely to receive diuretics and less comorbidities
- Lower values of Nt pro BNP


HFrEF
HFmrEF
HFpEF
Phenotype
Age
↑
↑↑
↑↑↑
Women
↓↓
↓
↑
Ischaemic heart disease
↑↑↑
↑↑↑
↑
Atrial fibrillation
↑
↑↑
↑↑↑
Hypertension
↑
↑↑
↑↑↑
Chronic kidney disease
↑↑
↑↑
↑↑↑
Natriuretic peptide levels
↑↑↑
↑
↑
Prognosis
Cardiovascular risk
↑↑↑
↑
↑
Non-cardiovascular risk
↑
↑
↑↑
Treatment
RAS inhibitors, β-Blockers, MRA, ARNI, SGLT2i
Relative effect
+++
+++
(Ongoing trials on MRA and SGLT2i)
±
Absolute effect
+++
+
(Ongoing trials on MRA and SGLT2i)
±
ICD, CRT
+++
±
±
HFrEF characteristics
HFpEF characteristics
Intermediate characteristics

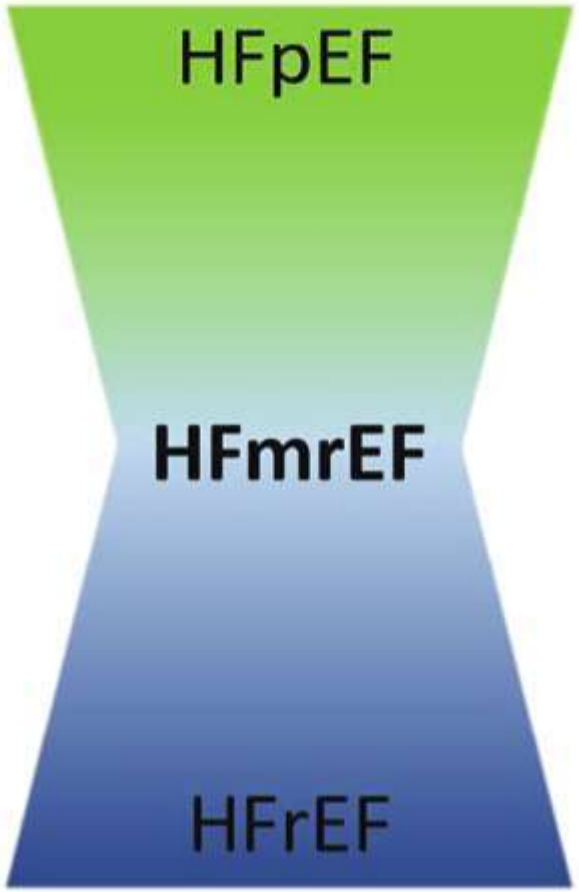
Study	EF type (%)[a]	Number of patients	Setting	Age (years)	Women (%)	SBP (mmHg)	CCS (%)	AF (%)	CKD (%)	eGFR (ml/min/ 1.73 m²)	BMI (kg/m²)	Diabetes mellitus (%)	NT-proBNP (pg/ml)
HFmrEF													
ESC-HF-LT[65]	24	2,212	Outpatient	64	32	127	42[c]	22	17	–	29	31	–
SwedeHF[48]	21	9,019	Both	74	39	131	53	58	48	62	27	27	2,160
GWTG-HF[75]	8	3,285	Inpatient	81	52	141	55	37	19	1.3[b]	27	42	5,054
OPTIMIZE-HF[74]	20	7,321	Inpatient	74	52	147	49[c]	33	–	1.3[b]	–	44	757[d]
ADHERE[76,e]	23	17,045	Inpatient	74	54	150	60	33	31	1.3[b]	30	48	–
TIME-CHF[69]	17	108	Outpatient	79	46	127	57[c]	40	64	49	26	40	3,941
CHART-2[70]	17	596	Outpatient	69	28	125	53[c]	44	–	59	23	36	165[d]
BIOSTAT-CHF[86]	18	416	Outpatient	75	34	129	48[f]	49	53	–	–	35	1,839

Breakthroughs in the treatment of heart failure with mildly reduced and preserved ejection fraction



Clinical Cardiology, Volume: 45, Issue: S1, Pages: S31-S39, First published: 05 July 2022, DOI: (10.1002/clc.23846)

A continuum of disease with some distinct features



HFmrEF features resembling HFpEF

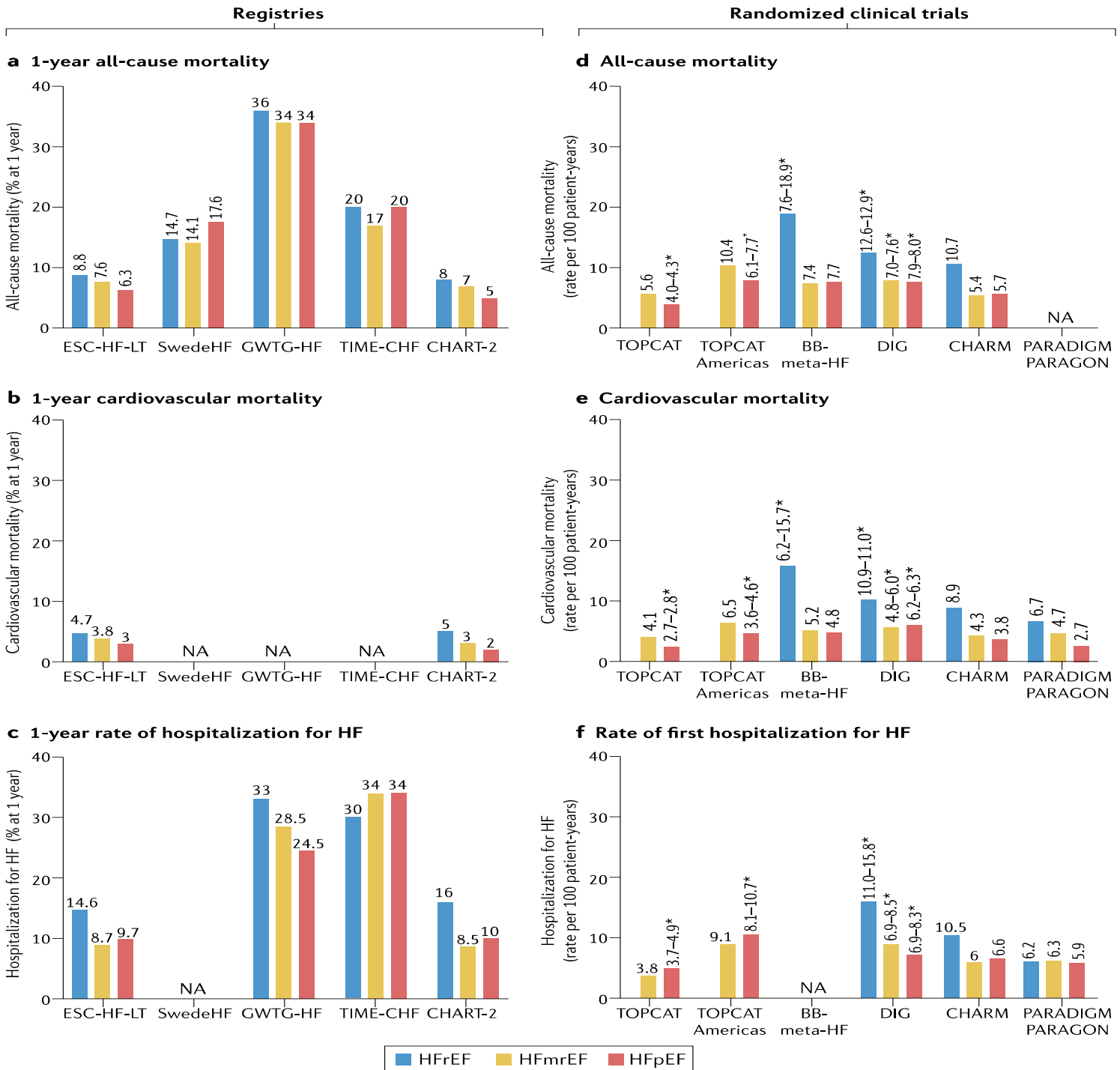
- Older age, Female sex
- Alchool use, potassium levels
- AF, Lung disease, Anemia
- HF hospitalization, deaths, combination of time to death/transplant and cardiac hospitalization, precipiting factors for in-hospital deaths

- Younger age, Male sex
- CAD, diabetes, valve disease
- Higher prognostic risk associated with CKD

HFmrEF features resembling HFrEF

Prognosis

- Two-year all-cause mortality in HFmrEF was 12% comparable to HFpEF and less than HFrEF(multi-ethnic cohort study)
- In the ESC-LT-HF Registry, observed one-year all-cause mortality was 7.6%, vs 6.3% in HFpEF and 8.8% in HFrEF
- Increased proportion of non-cardiovascular mortality whereas lower incidence of hospitalization for HF
- the incidence of all-cause mortality at ~3 years was 12.6% in HFmrEF (CHARM)


Registries
Randomized clinical trials
a 1-year all-cause mortality
All-cause mortality (% at 1 year)
8.8
7.6
6.3
14.7
14.1
17.6
36
34
34
20
17
20
8
7
5
ESC-HF-LT
SwedeHF
GWTG-HF
TIME-CHF
CHART-2
d All-cause mortality
All-cause mortality (rate per 100 patient-years)
5.6
4.0–4.3*
10.4
6.1–7.7*
7.6–18.9*
7.4
7.7
12.6–12.9*
7.0–7.6*
7.9–8.0*
10.7
5.4
5.7
NA
TOPCAT
TOPCAT Americas
BB-meta-HF
DIG
CHARM
PARADIGM PARAGON
b 1-year cardiovascular mortality
Cardiovascular mortality (% at 1 year)
4.7
3.8
3
NA
NA
NA
5
3
2
e Cardiovascular mortality
Cardiovascular mortality (rate per 100 patient-years)
4.1
2.7–2.8*
6.5
3.6–4.6*
6.2–15.7*
5.2
4.8
10.9–11.0*
4.8–6.0*
6.2–6.3*
8.9
4.3
3.8
6.7
4.7
2.7
c 1-year rate of hospitalization for HF
Hospitalization for HF (% at 1 year)
14.6
8.7
9.7
NA
33
28.5
24.5
30
34
34
16
8.5
10
f Rate of first hospitalization for HF
Hospitalization for HF (rate per 100 patient-years)
3.8
3.7–4.9*
9.1
8.1–10.7*
NA
11.0–15.8*
6.9–8.5*
6.9–8.3*
10.5
6
6.6
6.2
6.3
5.9
HFrEF
HFmrEF
HFpEF

Management Strategies

- In CHARM, candesartan reduced the primary outcome and the risk of recurrent HF hospitalizations in HFmrEF

- In the TOPCAT study, a significant interaction between EF and outcome was observed both for the primary composite endpoint of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest and for the secondary endpoint of HF hospitalizations, with potential efficacy in the lower EF range in the trial

- Meta-analysis of 11 RCT on betablockers demonstrated a treatment benefit for patients in sinus rhythm across the entire spectrum of EF. The hazard ratio for cardiovascular mortality in HFmrEF patients was 0.48 (95% CI 0.24–0.97)

- In 2020, in the PARAGON-HF trial involving patients with HF with EF ≥45%, treatment with sacubitril– valsartan was effective in patients with EF equal to or below the median (EF ≤57%)

- EMPEROR-Preserved study has become the first RCT that provided solid evidence of benefit in the treatment of HFpEF ,with a 21% reduction in cardiovascular mortality/HF hospitalization in the treatment arm compared to the placebo group, although with not significant effect on mortality. With an EF threshold for inclusion of >40%, one-third of the trial population had HFmrEF.

- In the SOLOIST-WHF trial, patients with HF and type 2 diabetes, The benefits of sotagliflozin for risk reduction of cardiovascular death or hospitalizations or urgent visits for HF was consistent in patients with EF <50% or ≥50%

- In SCD-HeFT trial, the subsequent benefit in reduced mortality that was gained by receiving an ICD was similar in patients who improved to EF >35% and those with persisting EF ≤35%.

- Patients who did not fulfil the criteria for an ICD had an annual rate of appropriate ICD interventions of around 3%(although lower in pts with persisting ICD indication)

- Available evidence suggests that the risk of arrhythmia persists at least to some extent in patients with improved or recovered EF.

Study	Total subjects (n)	Endpoints	LVEF (%)		Hazard ratio (95% CI)
CHARM-Preserved	1322	CVM or HFH	40-49		0.76 (0.60-0.96)
		Recurrent HFH	40-49		0.48 (0.33-0.70)
PEP-CHF	850	ACM or HFH	40-49		0.92 (0.70-1.21)
DIG (ancillary)	1195	CVM or HFH	40-49		0.96 (0.79-1.17)
		HF death or HFH	40-49		0.83 (0.66-1.05)
PEACE	2512	CVM	40-49		0.88 (0.72-1.09)
		HFH	40-49		0.96 (0.78-1.19)
TOPCAT	520	CVM, CA or HFH	<50		0.72 (0.50-1.05)
		HFH	<50		0.76 (0.46-1.27)
TOPCAT Americas	197	CVM, CA or HFH	<50		0.55 (0.33-0.91)
		HFH	<50		0.60 (0.32-1.10)
BB-META-HF	575	CVM	40-49		0.48 (0.24-0.97)
		CVM or CV hospitalization	40-49		0.83 (0.60-1.13)
PARAGON-PARADIGM	1427	CVM or HFH	42.5-52.5		0.89 (0.70-1.10)
		Total HFH	42.5-52.5		0.77 (0.58-1.02)
EMPEROR-Preserved	1983	CVM or HFH	<50		0.71 (0.57-0.88)

Clinical Cardiology, Volume: 45, Issue: S1, Pages: S31-S39, First published: 05 July 2022, DOI: (10.1002/clc.23846)

EMPEROR-PRESERVED

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker et al, Aug 27, 2021. NEJM.

QUESTION

In patients with heart failure and a preserved ejection fraction, does Empagliflozin improve outcomes?

INCLUDED

- 18 and older
- NYHA II-IV
- LVEF > 40%
- ntProBNP>300; or>900 if AFib
- Evidence of LAE or LVH
- Stable diuretic use
- BMI <45 kg/m2

5988 PATIENTS

EMPAGLIFLOZIN 10MG
(SGLT-2 INHIBITOR)

VS

PLACEBO

Stratified by region, diabetes status, eGFR of 50, and LVEF 50%

PRIMARY OUTCOME

CV Death*
HF Hospitalization

13.8%

17.1%

HR 0.79; 95%CI 0.69-0.90; P<0.001

*Mostly driven by HF hospitalizations

SECONDARY OUTCOMES

HF Hospitalization

↓ WITH EMPAGLIFLOZIN

HR 0.73; 95% CI, 0.61-0.88; P<0.001

Rate of GFR decline

E -1.25 vs. -2.62 P

ml/min/1.73m2/year; P<0.001

CONCLUSION

Empagliflozin reduced the combined risk of cardiovascular death or heart failure hospitalization in patients with heart failure with preserved ejection fraction, regardless of the presence or absence of diabetes.

@IsaMathiasMD

SOLOIST - WHF TRIAL

Bhatt DL et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-128.

SOTAGLIFLOZIN

inhibits

SGLT-2 ↓ increases urinary glucose excretion

SGLT-1 ↓ delays intestinal glucose absorption

QUESTION

In patients with diabetes and recently worsening HF, does SOTAGLIFLOZIN:

↓ CV mortality?

↓ HF urgent visits?

↓ HF hospitalizations?

INCLUSION

18 - 85 yo patients with diabetes hospitalized for signs or symptoms of HF and treatment with IV diuretics

1222 patients

	PRIMARY OUTCOME: HF urgent visits + HF hospitalizations + CV Death	SECONDARY OUTCOME: HF urgent visits + HF hospitalizations	SECONDARY OUTCOME: CV Death
	TOTAL NO. OF EVENTS (RATE PER 100 PATIENT YEARS)		
Sotagliflozin n=608	245 (51)	194 (40)	51 (11)
	HR 0.67 95% CI 0.52-0.85 p<0.001	HR 0.64 95% CI 0.49-0.83 p<0.001	HR 0.84 95% CI 0.58-1.22 p=0.36
Placebo n=614	355 (76)	297 (64)	58 (13)

CONCLUSION

In patients with diabetes with worsening HF, sotagliflozin significantly decreased CV deaths, HF urgent visits, and HF hospitalizations

Created by @TDonisan | @CardioNerdsJC

RESEARCH SUMMARY

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon SD et al. DOI: 10.1056/NEJMoa2206286

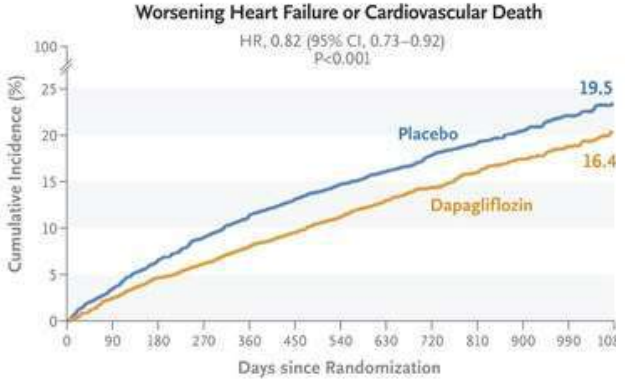
CLINICAL PROBLEM

Clinical guidelines recommend the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with chronic heart failure and a reduced ejection fraction (a left ventricular ejection fraction of ≤40%), but the benefits in patients with a higher ejection fraction are less certain.

CLINICAL TRIAL

Design: An international, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with stabilized heart failure and a mildly reduced or preserved ejection fraction.

Intervention: 6263 patients 40 years of age or older with a left ventricular ejection fraction of more than 40% were assigned to receive either dapagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death.



RESULTS

Efficacy: Overall, during a median follow-up of 2.3 years, a primary-outcome event occurred in significantly fewer patients in the dapagliflozin group than in the placebo group. A similar benefit was observed in a subgroup of patients with a left ventricular ejection fraction of less than 60%.

Safety: The incidence of serious adverse events was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Less than 5% of the patients enrolled were Black.
- All the subgroups were underpowered, so findings within subgroups should be interpreted with caution.
- Trials in higher-risk populations, or of longer duration, are needed to better assess the benefits of dapagliflozin with respect to mortality.

CONCLUSIONS

The SGLT2 inhibitor dapagliflozin reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction, with no excess of adverse events.

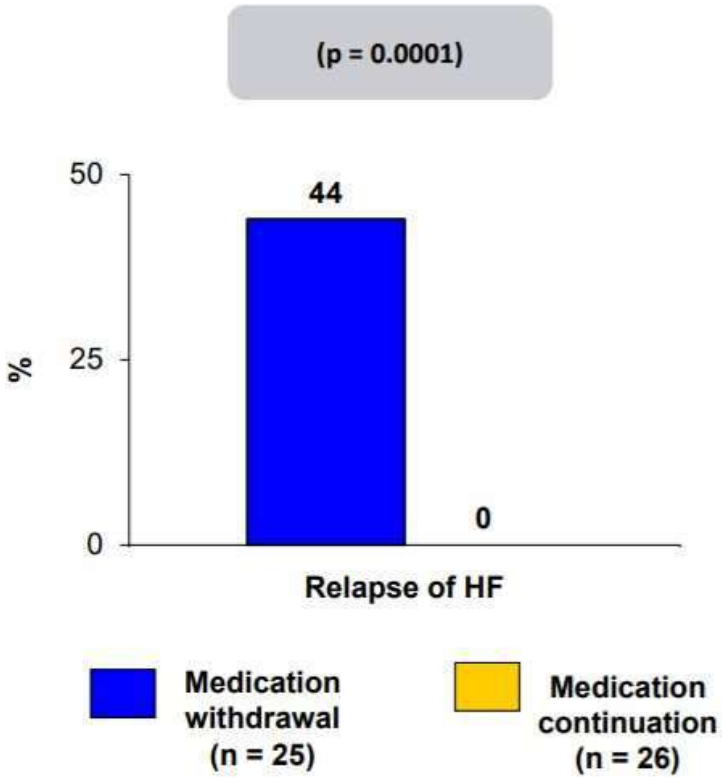
Links: Full Article | NEJM Quick Take | Editorial

TRED-HF

#AHA18

AMERICAN COLLEGE of CARDIOLOGY

Trial description: Patients with dilated cardiomyopathy who had recovered their LVEF were randomized in a 1:1 fashion to either HF medication withdrawal or medication continuation. Patients were followed for 6 months.



RESULTS

- Relapse of HF: drug withdrawal vs. continuation: 44% vs. 0%, p = 0.0001
- Death: 0% vs. 0%
- All relapsed patients were asymptomatic

CONCLUSIONS

- Withdrawal of HF medications among patients with dilated cardiomyopathy who had recovered their LV function results in relapse of HF, and should probably be avoided unless necessary and until predictors of relapse can be better outlined

Halliday BP, et al. Lancet 2018;Nov 11:[Epub]

DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

CHARITÉ

Aldosterone Blockade in HFmrEF/HFpEF:

SPIRonolactone in the Treatment of Heart Failure with mid-range and preserved Ejection Fraction (SPIRIT-HF)

Sponsor: Charité Universitätsmedizin Berlin
Funded by DZHK (German Center for Cardiovascular Research)

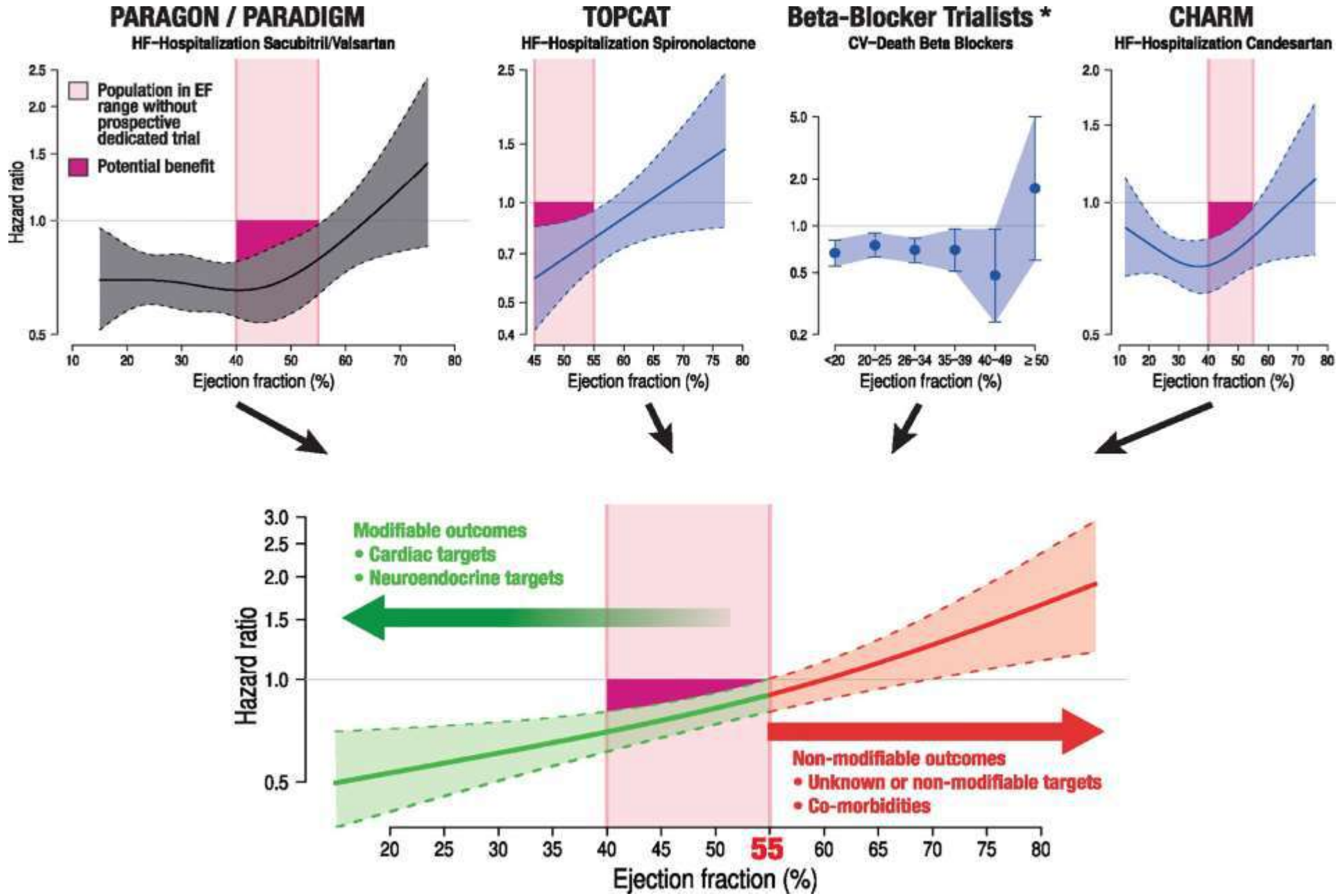
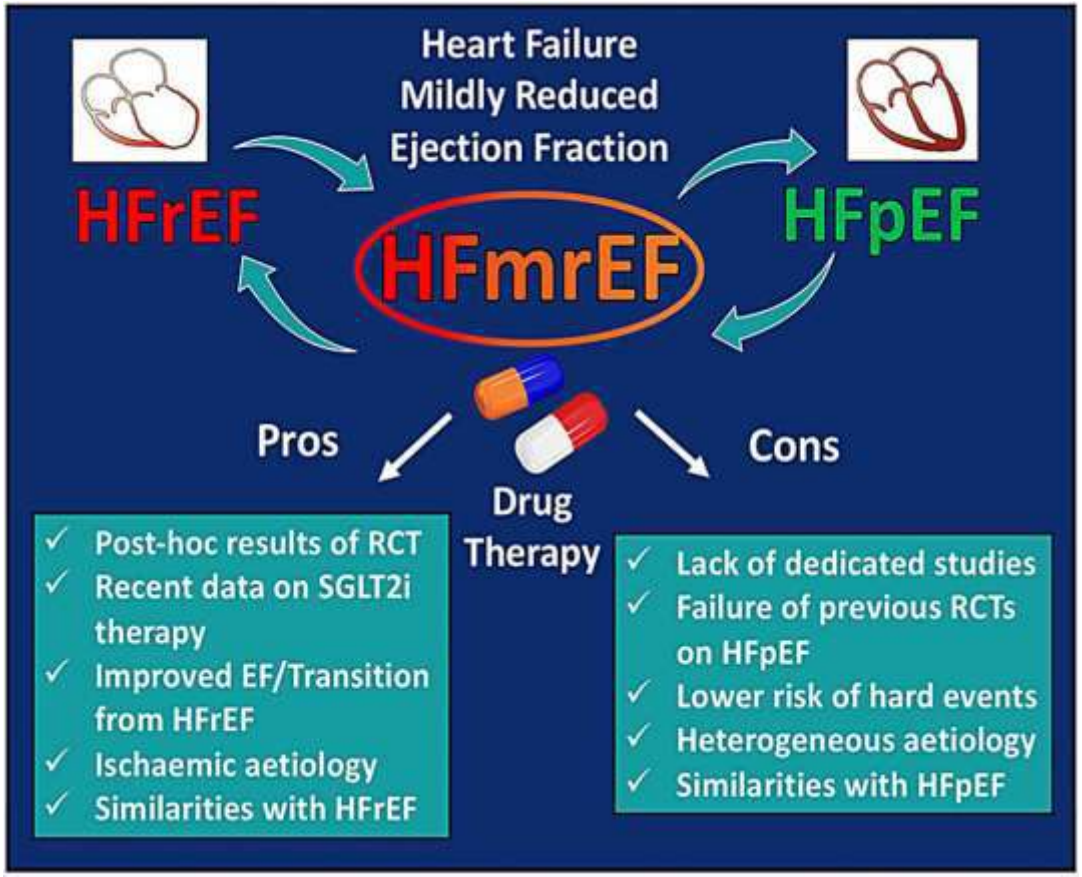

PARAGON / PARADIGM
HF–Hospitalization Sacubitril/Valsartan
Population in EF range without prospective dedicated trial
Potential benefit
Hazard ratio
Ejection fraction (%)
TOPCAT
HF–Hospitalization Spironolactone
Ejection fraction (%)
Beta-Blocker Trialists *
CV–Death Beta Blockers
<20 20–25 26–34 35–39 40–49 ≥50
Ejection fraction (%)
CHARM
HF–Hospitalization Candesartan
Ejection fraction (%)
Modifiable outcomes
• Cardiac targets
• Neuroendocrine targets
Non-modifiable outcomes
• Unknown or non-modifiable targets
• Co-morbidities
Hazard ratio
55
Ejection fraction (%)

Table 1 | **Major phase III randomized, controlled trials including patients with HF with EF of 40–49%**

Study	Year	Number of patients	Drug	Class	EF range (%)	Main HF category focus	Primary outcome	Follow-up (months)	Refs
ANZ	1997	415	Carvedilol	β-Blocker	<45	HFrEF	Death, hospitalization for HF or worsening HF	19	165
CHARM-Preserved	2003	3,023	Candesartan	ARB	>40	HFpEF	Cardiovascular death or first hospitalization for HF	37	51
SENIORS	2005	2,135	Nebivolol	β-Blocker	All	HFrEF	All-cause mortality, hospitalization for cardiovascular causes	21	147
PEACE	2004	8,290	Perindopril	ACEi	>40	HFpEF	Cardiovascular mortality, MI or revascularization	58	166
PEP-CHF	2006	850	Perindopril	ACEi	LVWMI 1.4–1.6	HFmrEF and HFpEF	All-cause mortality, hospitalization for HF	26	146
DIG (ancillary)	2006	988	Digoxin	–	>45	HFpEF	HF mortality, hospitalization for HF	37	167
I-PRESERVED	2008	4,128	Irbesartan	ARB	≥45	HFpEF	All-cause mortality or hospitalization for cardiovascular causes	49	58
MIRACLE-EF	2012	44	CRT pacemaker	Devices	36–50	HFmrEF	Death or first hospitalization for HF	Stopped early	168
TOPCAT	2014	3,445	Spironolactone	MRA	≥45	HFpEF	Cardiovascular death, aborted cardiac arrest or first hospitalization for HF	40	57
J-DHF	2014	245	Carvedilol	β-Blocker	>40	HFpEF	Cardiovascular death or first hospitalization for HF	39	169
PARAGON-HF	2019	4,822	Sacubitril–valsartan	ARNI	≥45	HFpEF	Cardiovascular death or total hospitalizations for HF	35	59
VICTORIA	2020	5,050	Vericiguat	sGC stimulator	<45	HFrEF	Cardiovascular death or first hospitalization for HF	11	29
SOLOIST-WHF	2021	1,222	Sotagliflozin	SGLT2i	<50	HFrEF	Cardiovascular death, total hospitalizations for HF or urgent hospital visits for HF	9	60
SPIRRIT-HFpEF	2016–ongoing	3,200	Spironolactone	MRA	≥40	HFpEF	Cardiovascular death or first hospitalization for HF	Ongoing	55,56
SPIRIT-HF	2017–ongoing	1,300	Spironolactone	MRA	≥40	HFpEF	Cardiovascular death or total hospitalizations for HF	Ongoing	54
EMPEROR-Preserved	2017–ongoing	5,988	Empagliflozin	SGLT2i	>40	HFpEF	Cardiovascular death or first hospitalization for HF	Ongoing	148
EMPERIALPreserved	2018–ongoing	315	Empagliflozin	SGLT2i	>40	HFpEF	Changes in 6-min walking distance	Ongoing	149
DELIVER	2018–ongoing	6,100	Dapagliflozin	SGLT2i	>40	HFpEF	Cardiovascular death, first hospitalization for HF or urgent hospital visit for HF	Ongoing	53
DETERMINE-PRESERVED	2019–ongoing	504	Dapagliflozin	SGLT2i	>40	HFpEF	KCCQ-TSS changes	Ongoing	150
PARAGLIDE-HF	2019–ongoing	800	Sacubitril–valsartan	ARNI	>40	HFpEF	NT-proBNP changes	Ongoing	170
FINEARTS-HF	2020–ongoing	5,500	Finerenone	MRA	≥40	HFpEF	Cardiovascular death or total hospitalizations for HF	Ongoing	171

	ACEI	ARB	Beta-blocker	MRA	ARNI	SGLT2I	Diuretic
HFrEF	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	**?**
HFmrEF	**?**	↑	↑	↑	↑	**?**	**?**
HFpEF	**×**	↑	**×**	↑	↑	**?**	**?**

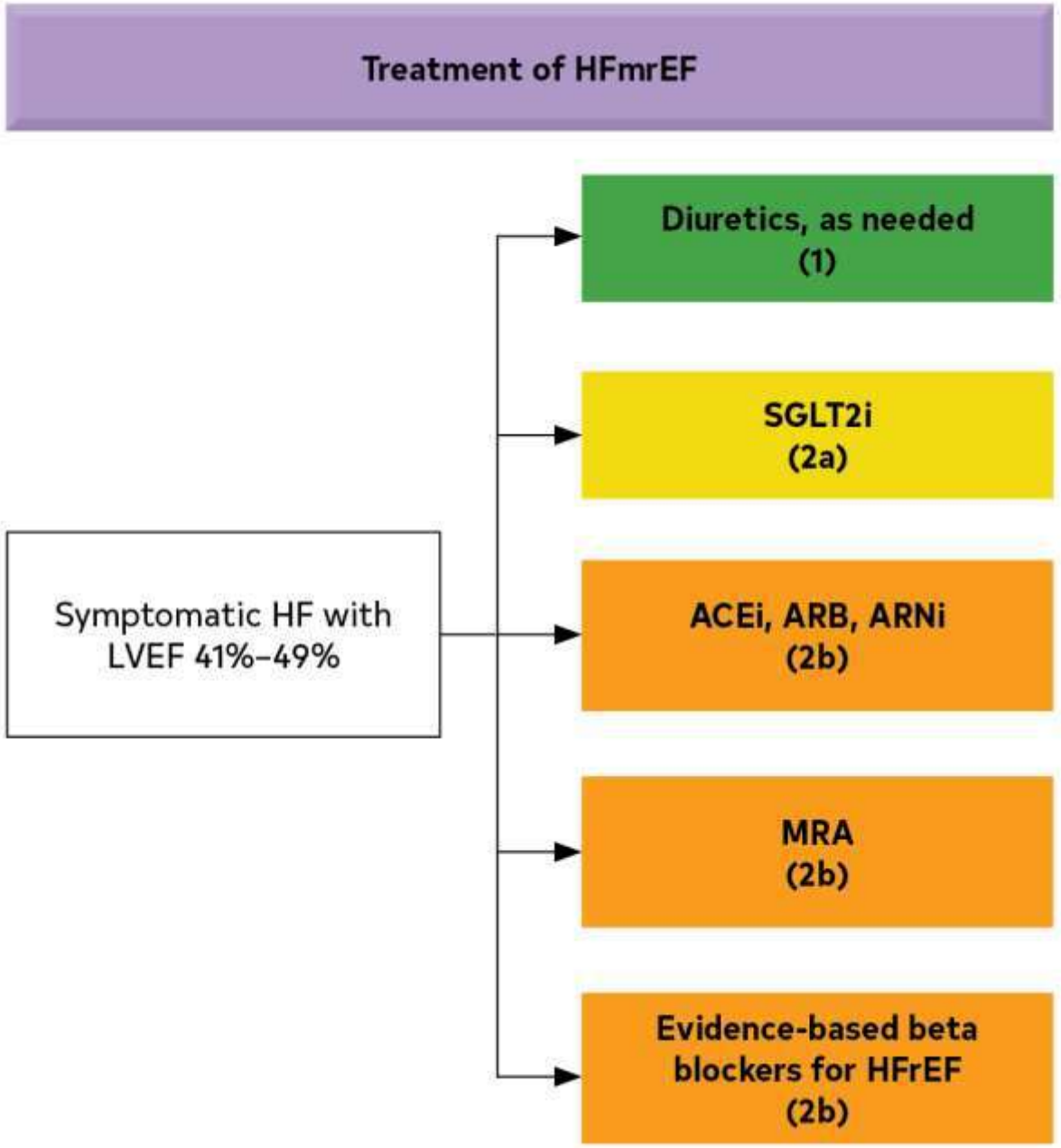
↑↑: Proven cardiovascular benefit.
↑: Potential cardiovascular benefit.
***×**: No cardiovascular benefit.*
***?**: Uncertain cardiovascular benefit.*
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ARNI, angiotensin receptor—neprilysin inhibitor; SGLT2I, sodium glucose cotransporter 2 inhibitors.



HF With Mildly Reduced Ejection Fraction

Recommendations for HF With Mildly Reduced Ejection Fraction Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
2a	**B-R**	**1. In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.**
2b	**B-NR**	**2. Among patients with current or previous symptomatic HFmrEF (LVEF 41%–49%), use of evidence-based beta blockers for HFrEF, ARNi, ACEi or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.**

Figure 11. Recommendations for Patients With Mildly Reduced LVEF (41%–49%)

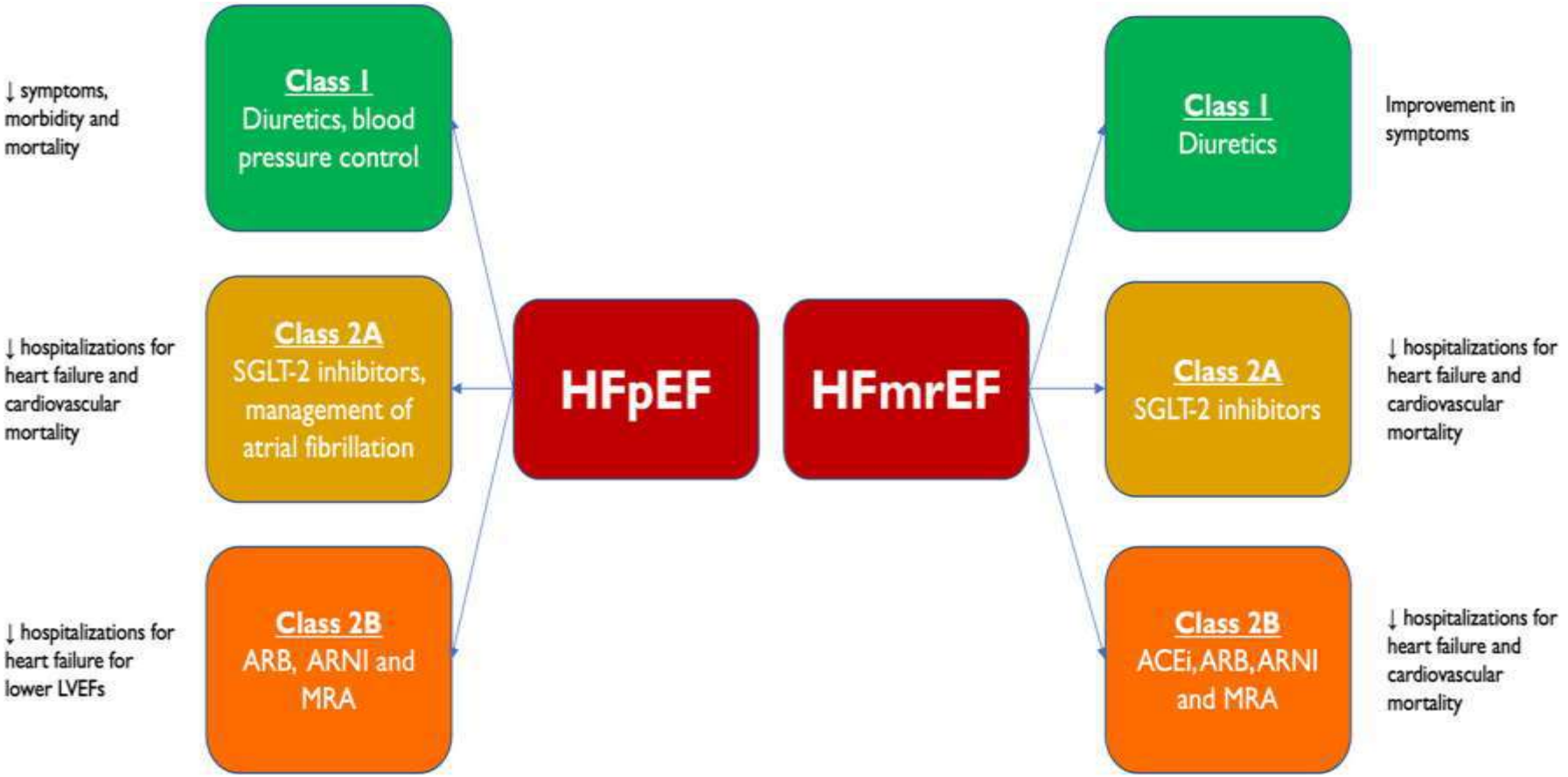


Colors correspond to COR in Table 2.

Medication recommendations for HFmrEF are displayed.

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HRmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium- glucose cotransporter 2 inhibitor.

Breakthroughs in the treatment of heart failure with mildly reduced and preserved ejection fraction



Clinical Cardiology, Volume: 45, Issue: S1, Pages: S31-S39, First published: 05 July 2022, DOI: (10.1002/clc.23846)

Take Home Message

HFmrEF comprises a heterogenous population of patients with distinct and heterogeneous prognostic profiles.

HFmrEF may occur either as a recovery from HFrEF or, less often, as a progression from HFpEF or may also be the first presentation of HF

The overall picture supports the notion that HFmrEF is more similar to HFrEF than to HFpEF, especially in aetiology and treatment response, and therefore is more appropriately termed HF with mildly reduced EF

Patients with HFmrEF seem to be responsive to HFrEF medications but the strength of recommendations and level of evidence for these drugs in patients with HFmrEF must be considered modest

Ongoing clinical trials in patients with HFmrEF, in particular of MRAs and SGLT2 inhibitors, will inform the future treatment landscape in HFmrEF.