Non-Ischemic Cardiomyopathy
Medical treatment following recent guidelines

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המכון לאי ספיקת לב, שיבא, תל השומר

SHEBA Tel HaShomer | The Leviev Cardiothoracic & Vascular Center

האיגוד הקרדיולוגי בישראל ISRAEL HEART SOCIETY

החוג לאי ספיקת לב THE ISRAEL WORKING GROUP ON HEART FAILURE

Non-Ischemic Cardiomyopathy

Ischemic Cardiomyopathy

Ischemic cardiomyopathy is diagnosed in patients with heart failure who have had an acute coronary syndrome or have evidence of hibernating myocardium or angiographically severe coronary disease.

Ischemic Cardiomyopathy

Non-ischemic cardiomyopathy is a general term which includes any cause of abnormal cardiac structure or function other than those caused by ischemic etiology.

Patients with single vessel disease who have no evidence of previous ischemic event that may explain the degree of ventricular dysfunction should be classified as non-ischemic cardiomyopathy

Table 5 **Causes of heart failure, common modes of presentation and specific investigations**

Cause	Examples of presentations	Specific investigations
CAD	Myocardial infarction Angina or "angina-equivalent" Arrhythmias	Invasive coronary angiography CT coronary angiography Imaging stress tests (echo, nuclear, CMR)
Hypertension	Heart failure with preserved systolic function Malignant hypertension/acute pulmonary oedema	24 h ambulatory BP Plasma metanephrines, renal artery imaging Renin and aldosterone
Valve disease	Primary valve disease e.g., aortic stenosis Secondary valve disease, e.g. functional regurgitation Congenital valve disease	Echo – transoesophageal/stress
Arrhythmias	Atrial tachyarrhythmias Ventricular arrhythmias	Ambulatory ECG recording Electrophysiology study, if indicated
CMPs	All Dilated Hypertrophic Restrictive ARVC Peripartum Takotsubo syndrome Toxins: alcohol, cocaine, iron, copper	CMR, genetic testing Right and left heart catheterization CMR, angiography Trace elements, toxicology, LFTs, GGT
Congenital heart disease	Congenitally corrected/repaired transposition of great arteries Shunt lesions Repaired tetralogy of Fallot Ebstein's anomaly	CMR
Infective	Viral myocarditis Chagas disease HIV Lyme disease	CMR, EMB Serology
Drug-induced	Anthracyclines Trastuzumab VEGF inhibitors Immune checkpoint inhibitors Proteasome inhibitors RAF+MEK inhibitors	
Infiltrative	Amyloid Sarcoidosis Neoplastic	Serum electrophoresis and serum free light chains, Bence Jones protein, Bone scintigraphy, CMR, CT-PET, EMB Serum ACE, CMR, FDG-PET, chest CT, EMB CMR, EMB
Storage disorders	Haemochromatosis Fabry disease Glycogen storage diseases	Iron studies, genetics, CMR (T2* imaging), EMB α-galactosidase A, genetics, CMR (T1 mapping)
Endomyocardial disease	Radiotherapy Endomyocardial fibrosis/eosinophilia Carcinoid	CMR EMB 24 h urine 5-HIAA
Pericardial disease	Calcification Infiltrative	Chest CT, CMR, Right and Left heart catheterisation
Metabolic	Endocrine disease Nutritional disease (thiamine, vitamin B1 and selenium deficiencies) Autoimmune disease	TFTs, plasma metanephrines, renin and aldosterone, cortisol Specific plasma nutrients ANA, ANCA, rheumatology review
Neuromuscular disease	Friedreich's ataxia Muscular dystrophy	Nerve conduction studies, electromyogram, genetics CK, electromyogram, genetics

2021 ESC HF Guidelines

Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

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(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

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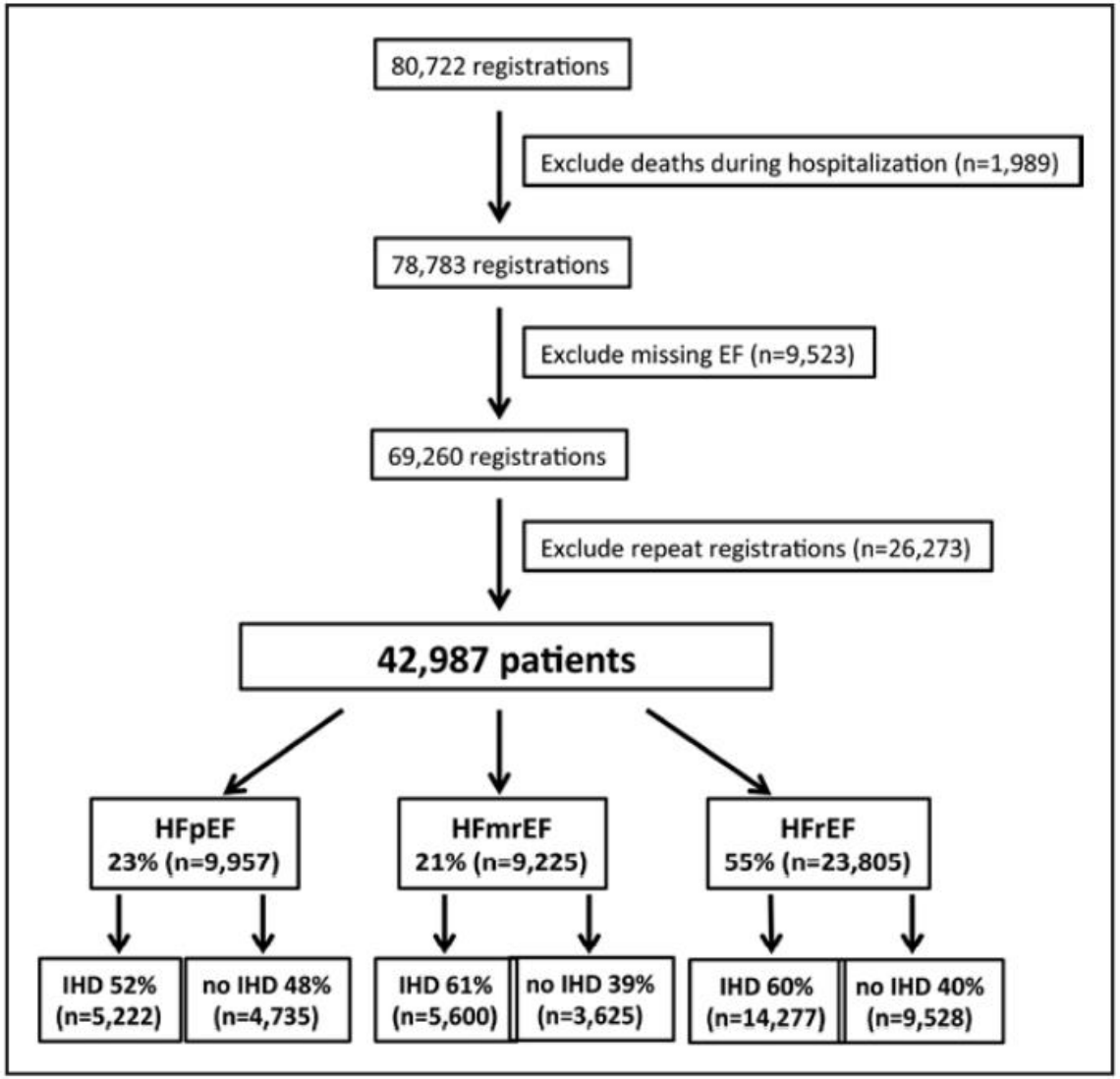
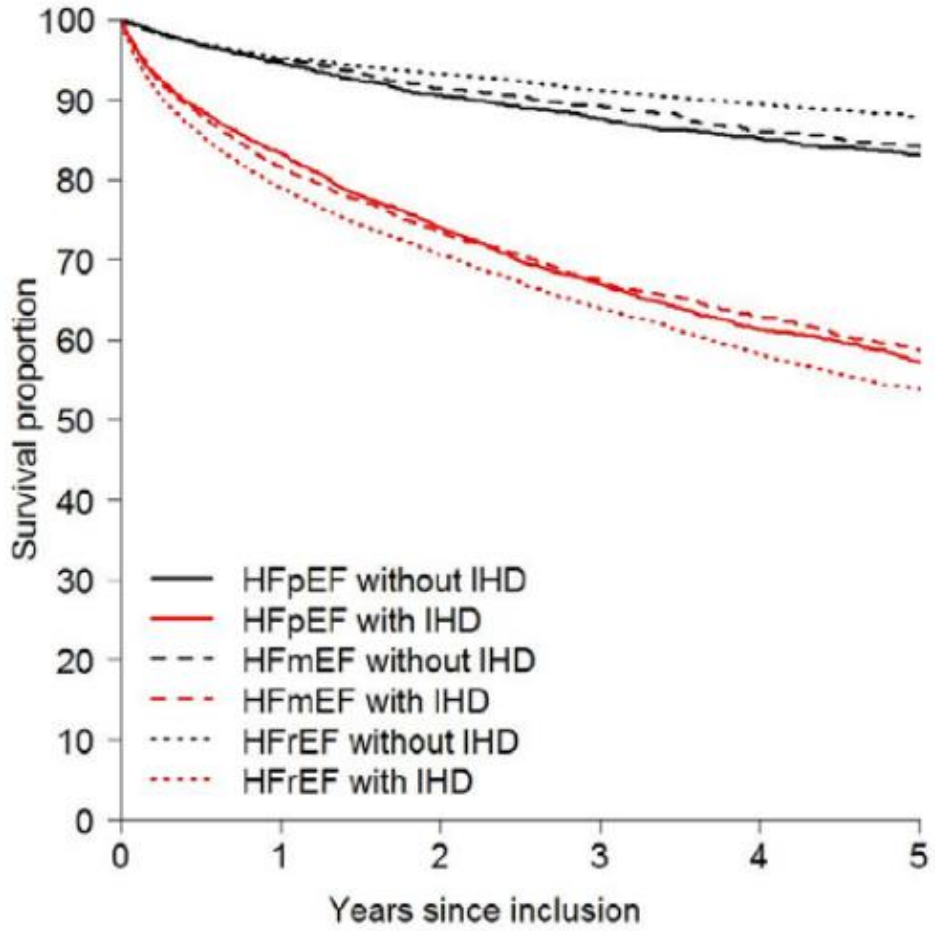
2021 ESC HF Guidelines

Ischemic vs. non-ischemic HF

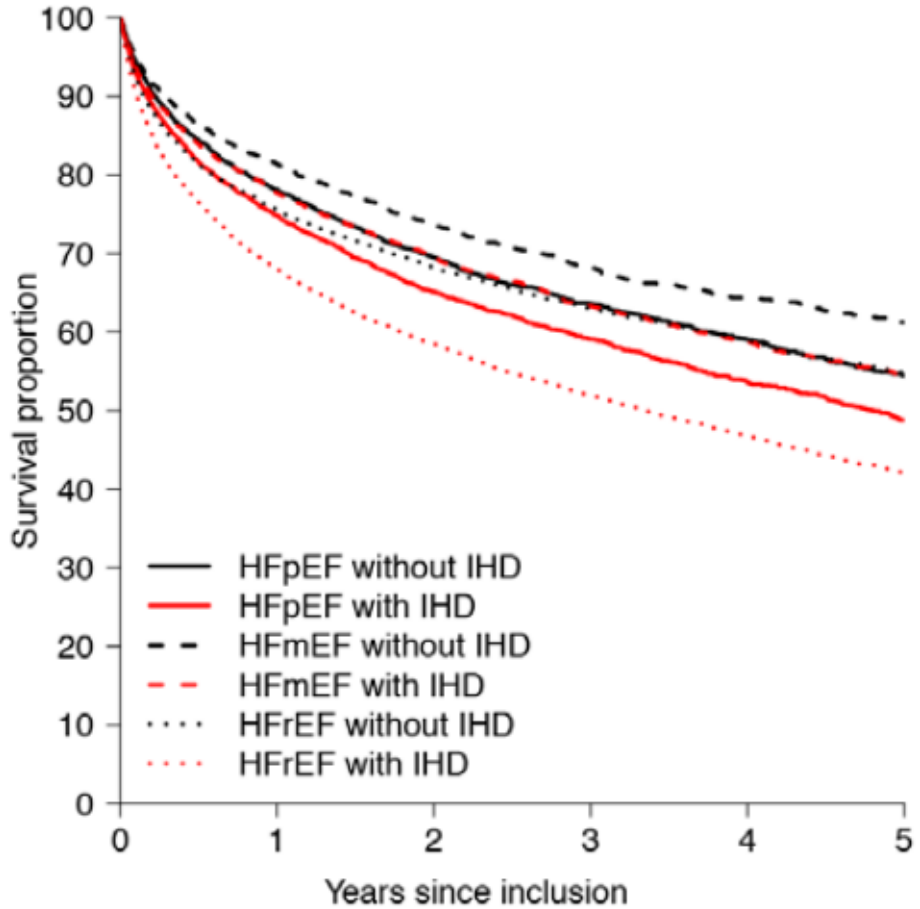


Vedin et al. Circ Heart Fail. 2017

Incidence of nonfatal and fatal IHD

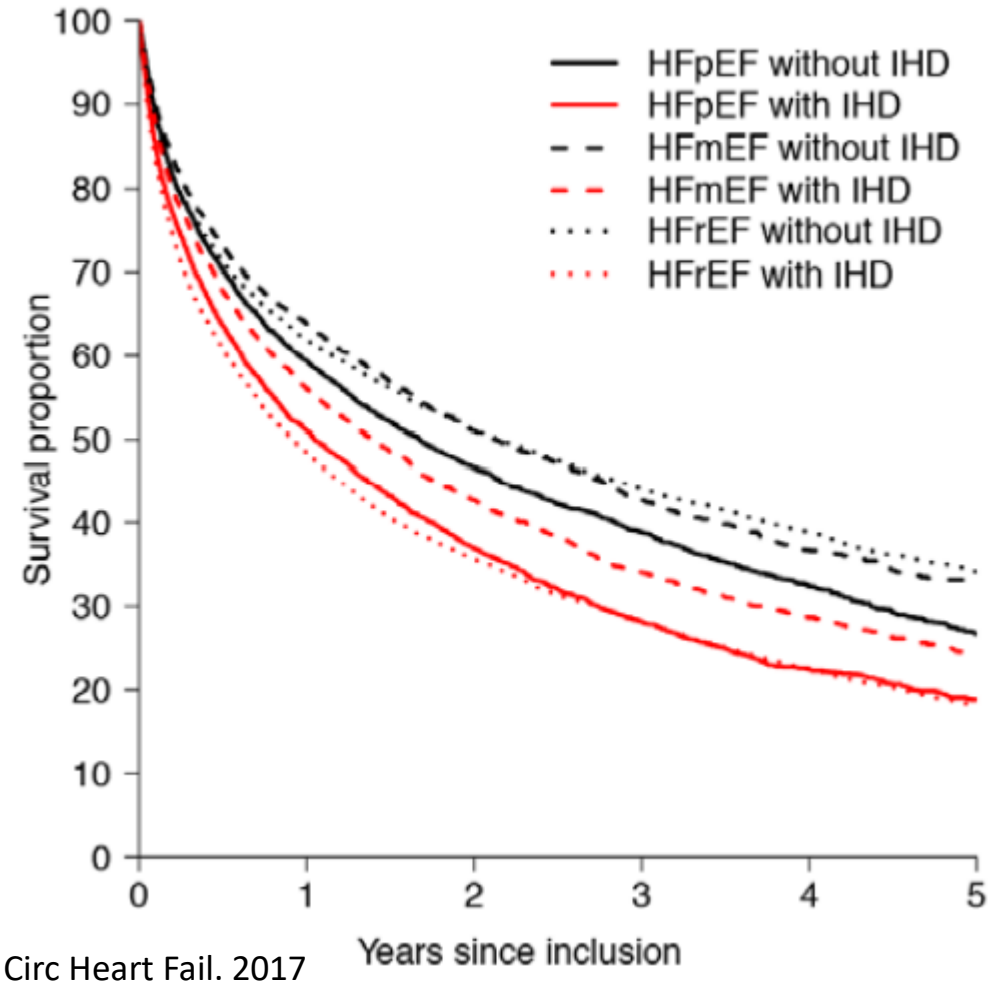


Incidence of nonfatal and fatal HF

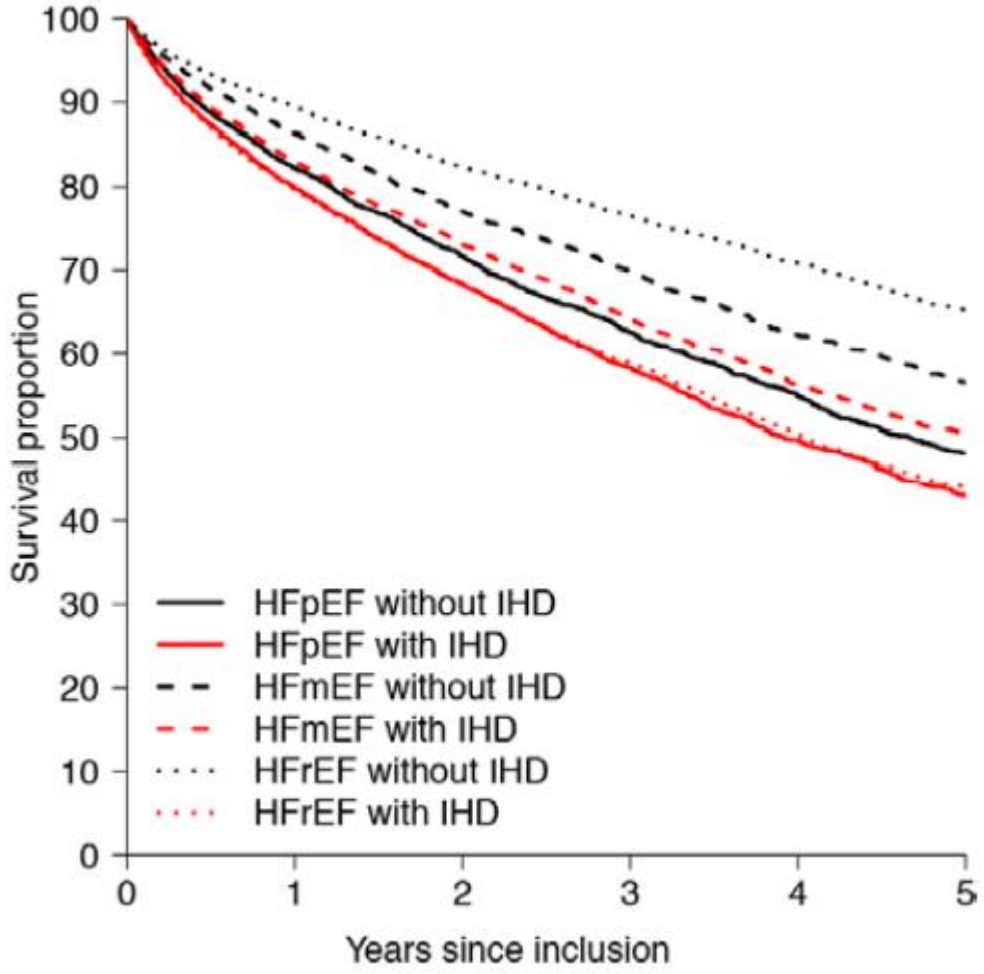


Vedin et al. Circ Heart Fail. 2017

Incidence of nonfatal and fatal CV events

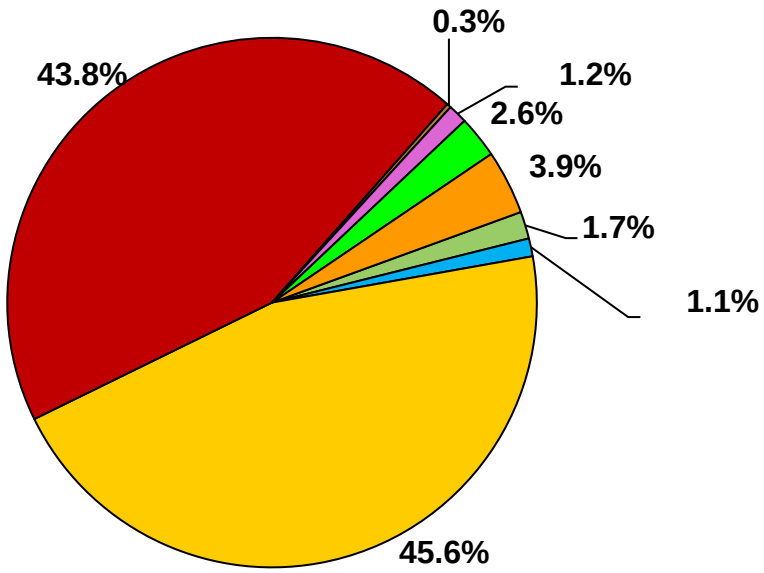


Incidence of all caused mortality

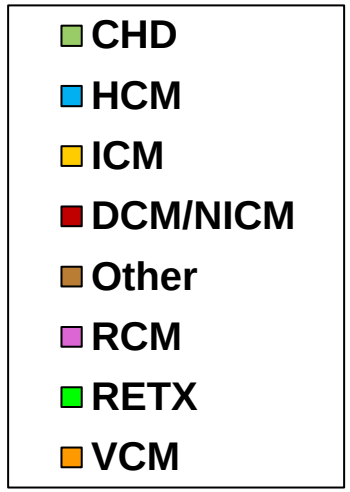


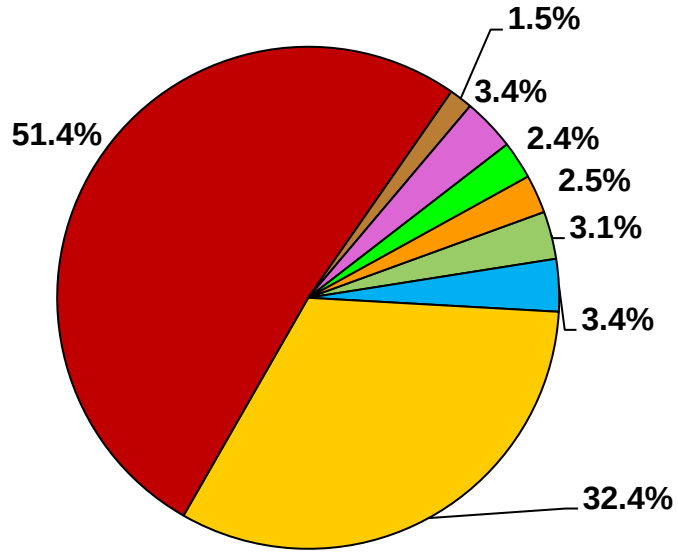
Vedin et al. Circ Heart Fail. 2017

Adult Heart Transplants
Diagnosis by Era

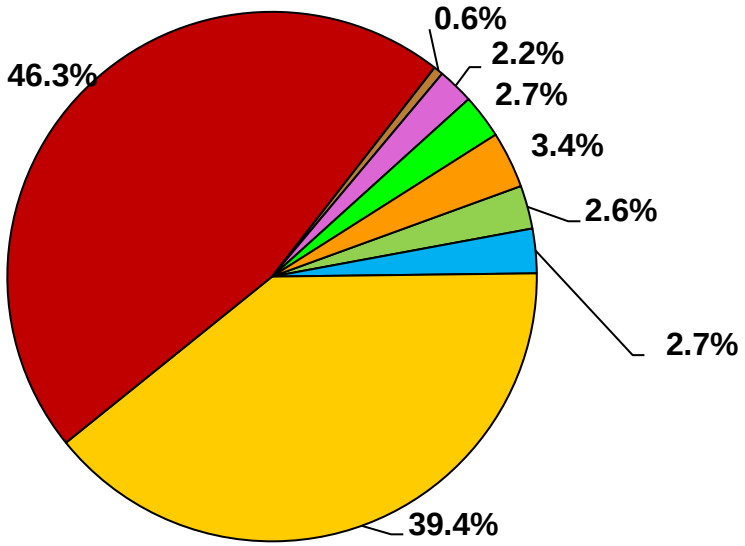


1992-2000





2010-2018

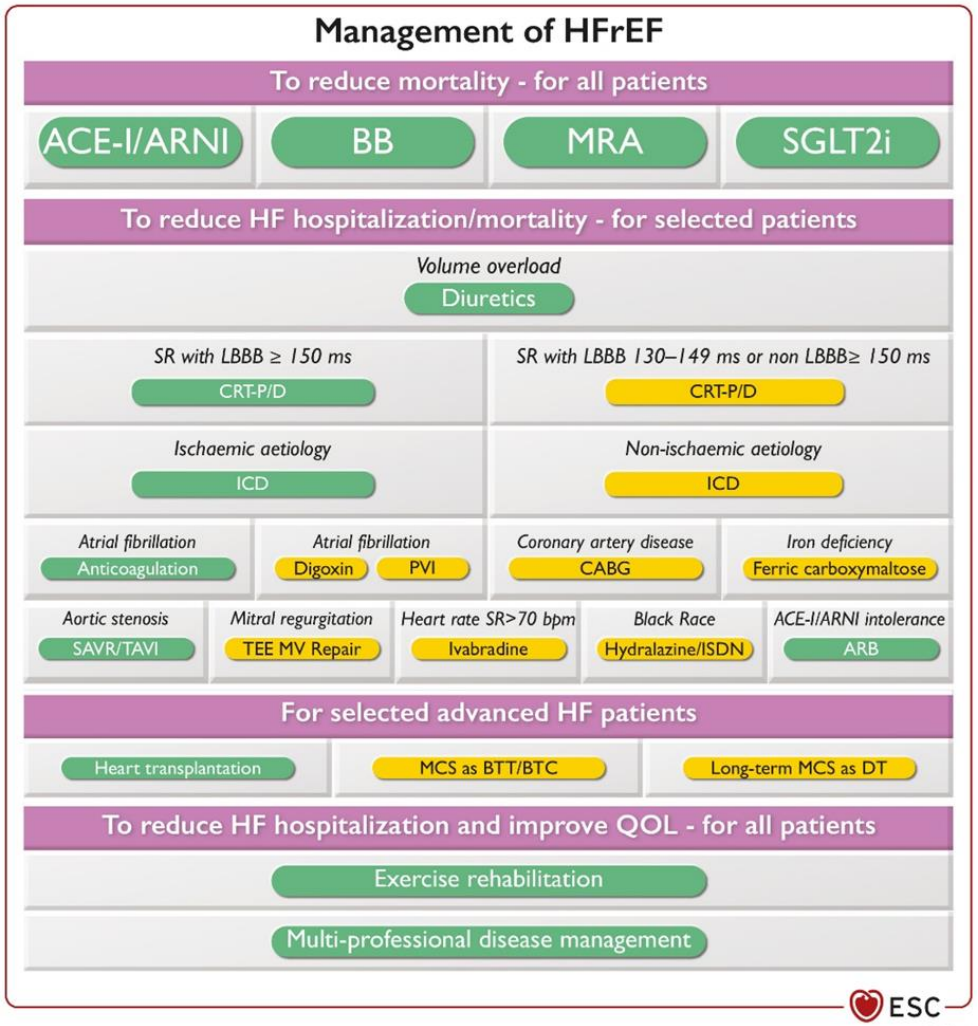


2001-2009

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2022
JHLT. 2022 Oct; 41(10): 1335-1375

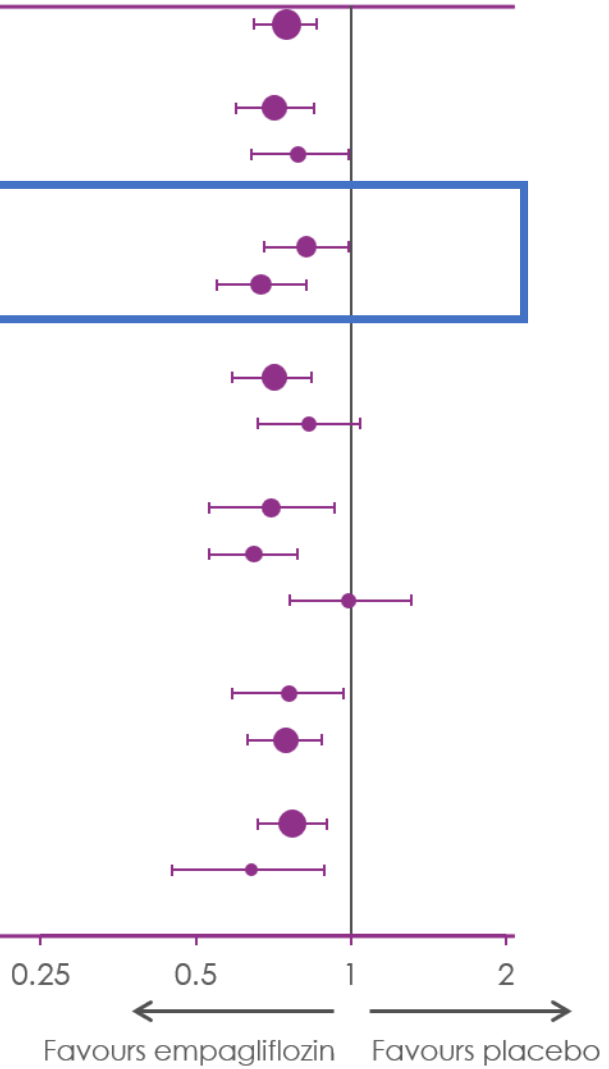
Non-Ischemic Cardiomyopathy medical treatment

HFrEF



Effect of Ischemic heart disease on HF therapy

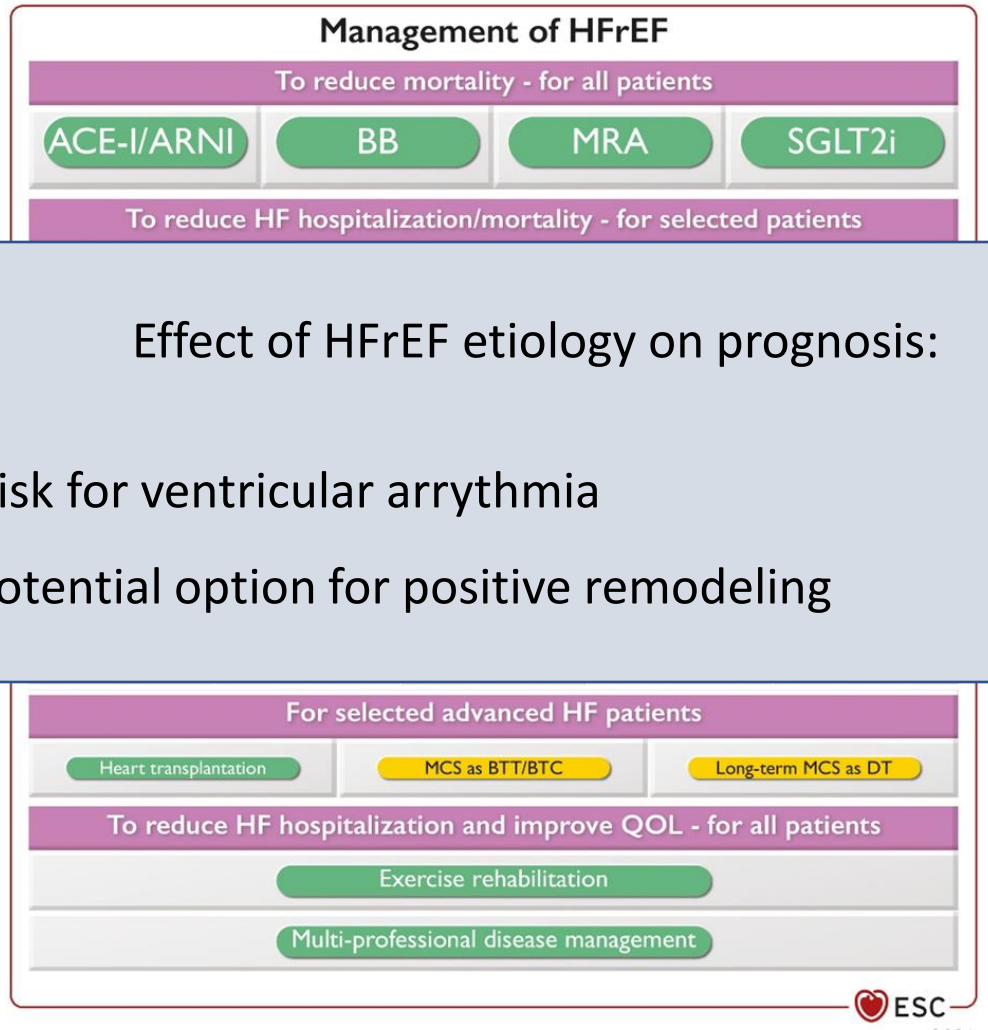
	Empagliflozin 10 mg	Placebo		
	n with event/N analysed		HR (95% CI)	HR (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)	
History of HF (in last 12 months)				
No	208/1286	285/1293	0.71 (0.60, 0.85)	
Yes	153/577	177/574	0.79 (0.64, 0.99)	
Cause of HF				
Ischaemic	207/983	236/946	0.82 (0.68, 0.99)	
Non-ischaemic	154/880	226/921	0.67 (0.55, 0.82)	
Baseline NYHA class				
II	220/1399	299/1401	0.71 (0.59, 0.84)	
III/IV	141/464	163/466	0.83 (0.66, 1.04)	
HF physiology*				
LVEF ≤30% and NTproBNP <median	80/699	115/724	0.70 (0.53, 0.93)	
LVEF ≤30% and NTproBNP ≥median	169/631	249/661	0.65 (0.53, 0.79)	
LVEF >30%	108/526	97/475	0.99 (0.76, 1.31)	
Baseline use of MRA				
No	118/557	132/512	0.76 (0.59, 0.97)	
Yes	243/1306	330/1355	0.75 (0.63, 0.88)	
Baseline use of ARNI				
No	310/1523	369/1480	0.77 (0.66, 0.90)	
Yes	51/340	93/387	0.64 (0.45, 0.89)	



*Interaction p=0.042
ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction;
MRA, mineralocorticoid receptor antagonists; NTproBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Non-Ischemic Cardiomyopathy medical treatment

HFrEF



Effect of HFrEF etiology on prognosis:

1. Risk for ventricular arrythmia
2. Potential option for positive remodeling

Recommendations for an implantable cardioverter-defibrillator in patients with heart failure

Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days–see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.	IIa	A

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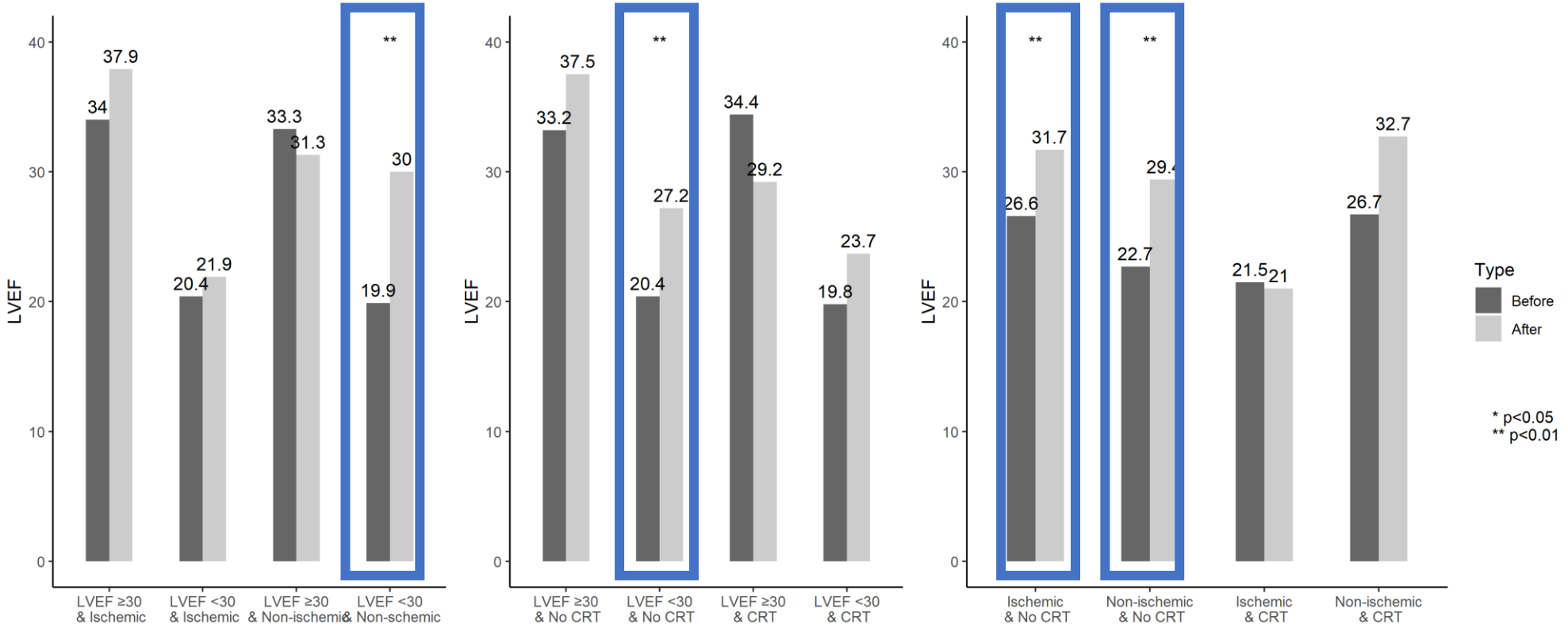
Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic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

Circulation, 2022; 145:e895-1032

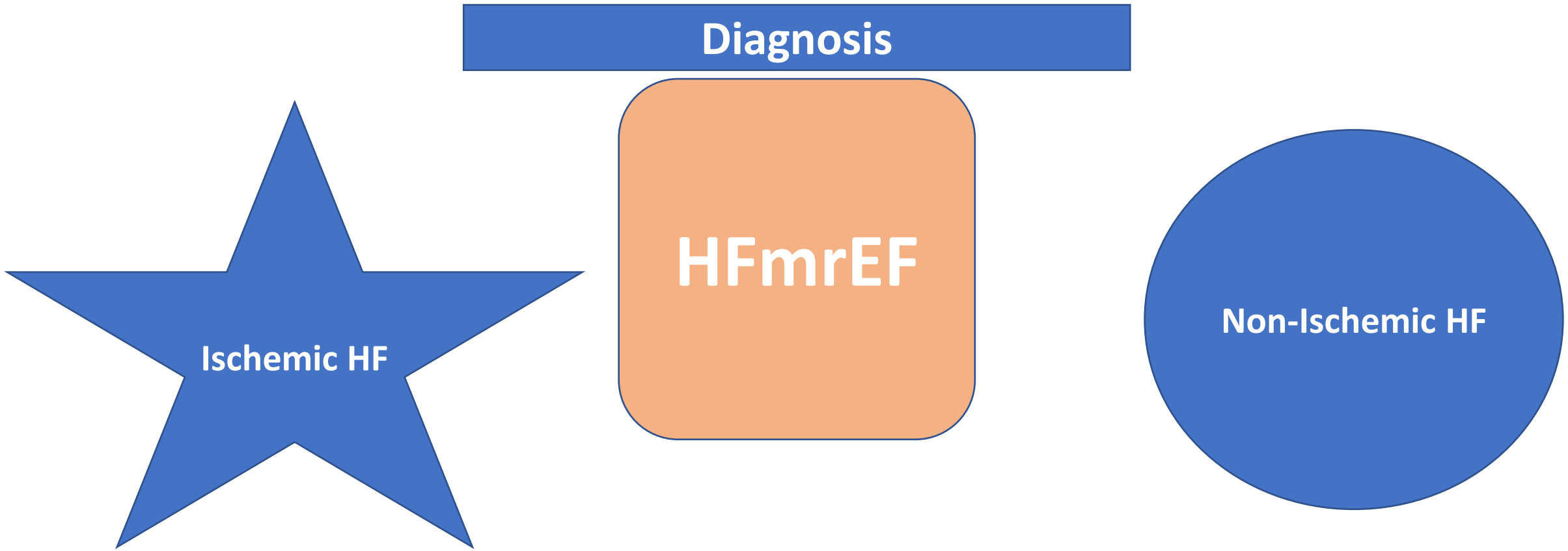
ESC Heart Failure
Open Access
HFA Heart Failure Association
ESC Heart Failure2022;9: 1682–1688

Characterization of heart failure patients with reverse left ventricular remodelling post-angiotensin receptor blockers/neprilysin inhibitors therapy

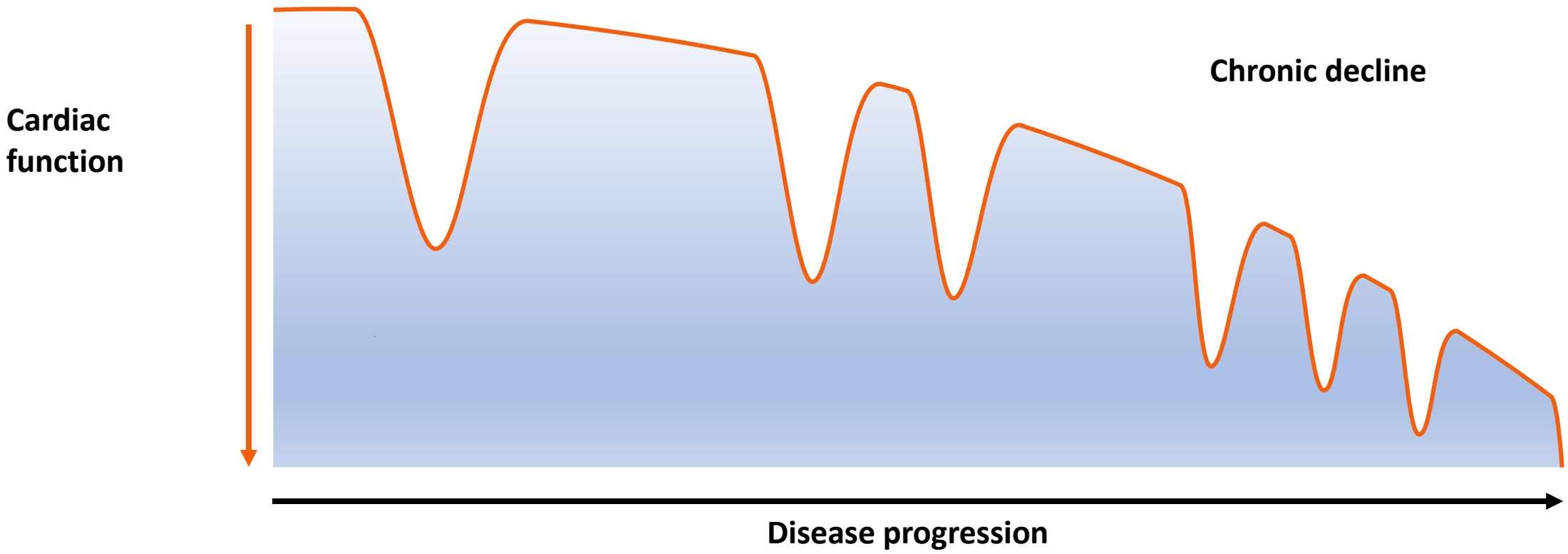
Leonid Maizels, Yishay Wasserstrum, Boris Fishman, Amitai Segev, David Ben-Nun, Anan Younis, Dov Freimark, Israel Mazin, Avishay Grupper



Non-Ischemic Cardiomyopathy medical treatment



Non-Ischemic Cardiomyopathy medical treatment



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.

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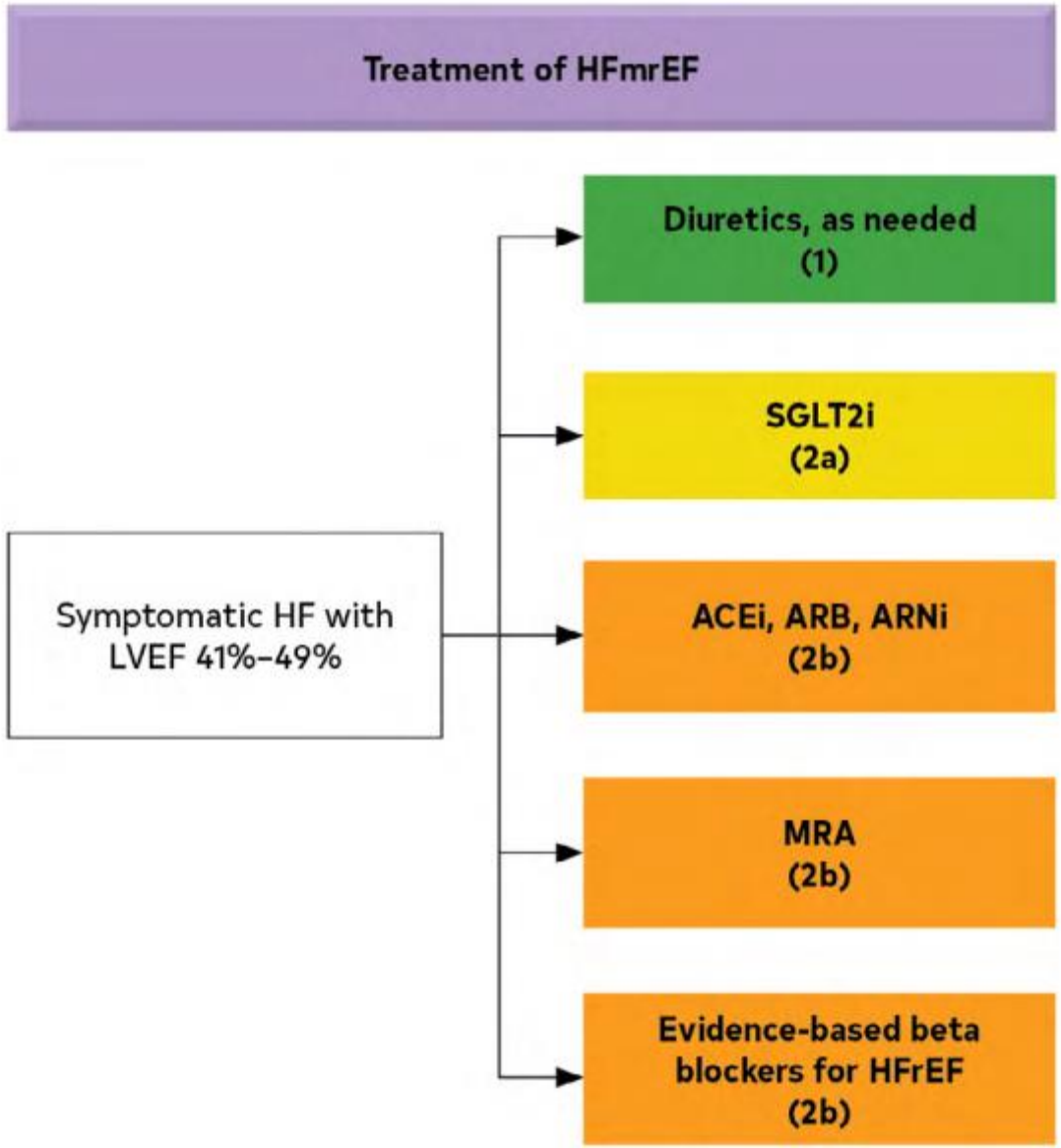
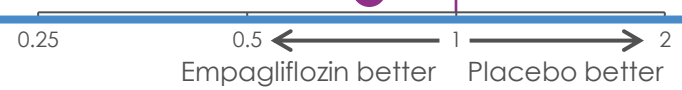


2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

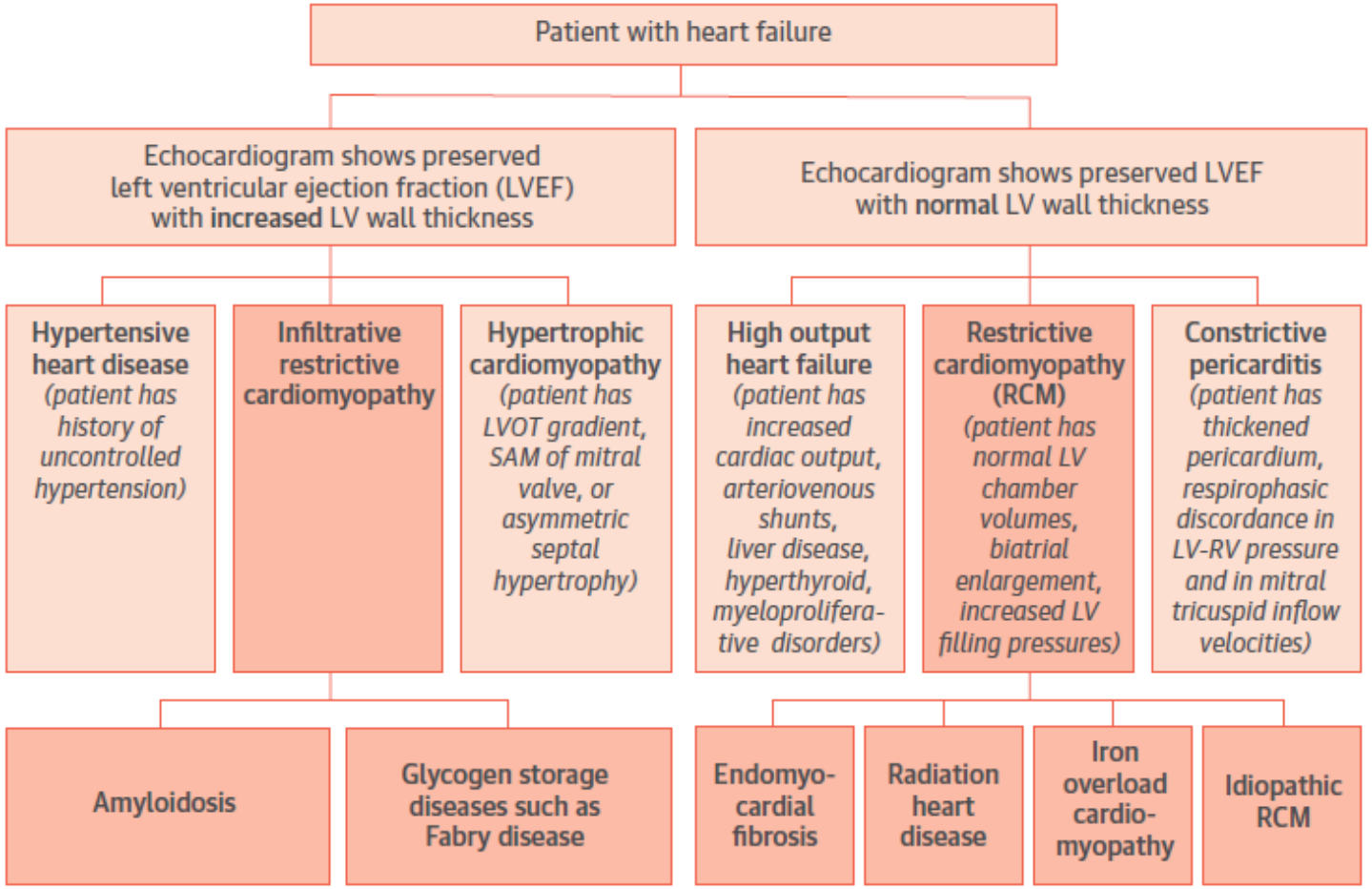
EMPEROR-Preserved: Primary endpoint subgroup analysis

	Empagliflozin	Placebo	HR (95% CI)	P value interaction[2]
	n with event/N analysed			
Overall	415/2997	511/2991	0.79 (0.69, 0.90)	
Baseline LVEF				0.2098
<50%	145/995	193/988	0.71 (0.57, 0.88)	
≥50% to <60%	138/1028	173/1030	0.80 (0.64, 0.99)	
≥60%	132/974	145/973	0.87 (0.69, 1.10)	
Baseline diabetes status				0.9224
Diabetes	239/1466	291/1472	0.79 (0.67, 0.94)	
No diabetes	176/1531	220/1519	0.78 (0.64, 0.95)	
Baseline eGFR (CKD-EPI)				0.7673
≥60 mL/min/1.73 m²	152/1493	189/1505	0.81 (0.65, 1.00)	
<60 mL/min/1.73 m²	263/1504	321/1484	0.78 (0.66, 0.91)	
Baseline NYHA class				0.3081
II	275/2435	361/2452	0.75 (0.64, 0.87)	
III/IV	140/562	150/539	0.86 (0.68, 1.09)	
HF hospitalization in ≤12 months				0.4441
No	258/2298	319/2321	0.81 (0.68, 0.95)	
Yes	157/699	192/670	0.73 (0.59, 0.90)	
Cause of HF				
Ischaemic	157/1079	177/1038	0.85 (0.69, 1.06)	0.1441
Non-ischaemic	258/1917	334/1953	0.75 (0.64, 0.89)	0.0006



CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association 1. Anker S *et al. N Engl J Med*. 2021; doi:10.1056/NEJMoa2107038; 2. Boehringer Ingelheim data on file.

Non-Ischemic Cardiomyopathy medical treatment



HFpEF

ESC 2021 recommendations for the treatment of HFpEF

	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF.	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.	I	C

[a]Class of recommendation. [b]Level of evidence.
ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.
McDonagh TA *et al. Eur Heart J.* 2021; doi:10.1093/eurheartj/ehab368.

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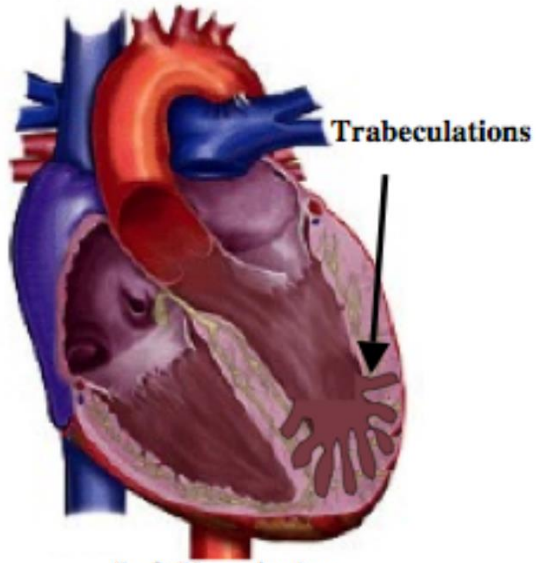
Circulation, 2022; 145:e895-1032

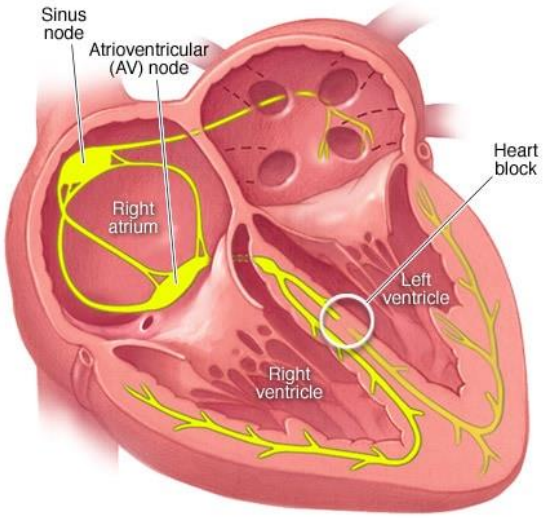
Recommendations for HF With Preserved Ejection Fraction*
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

Cardiac phenotypes with potential pathologic progression to cardiomyopathy



LBBB Cardiomyopathy



Summary

Significant coronary artery disease should be excluded during evaluation process of newly diagnosed HF to establish ischemic vs. non-ischemic etiology

The diagnosis of ischemic vs. non-ischemic HF may alter the estimated risk of potential complications and expected prognosis.

The specific cause of non-ischemic cardiomyopathy should be sought since disease-specific therapy is available for certain conditions.

Genetic and imaging studies should be considered to evaluate the risk and to diagnose non-ischemic cardiomyopathy in asymptomatic individuals at risk.

תודה על ההקשבה

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