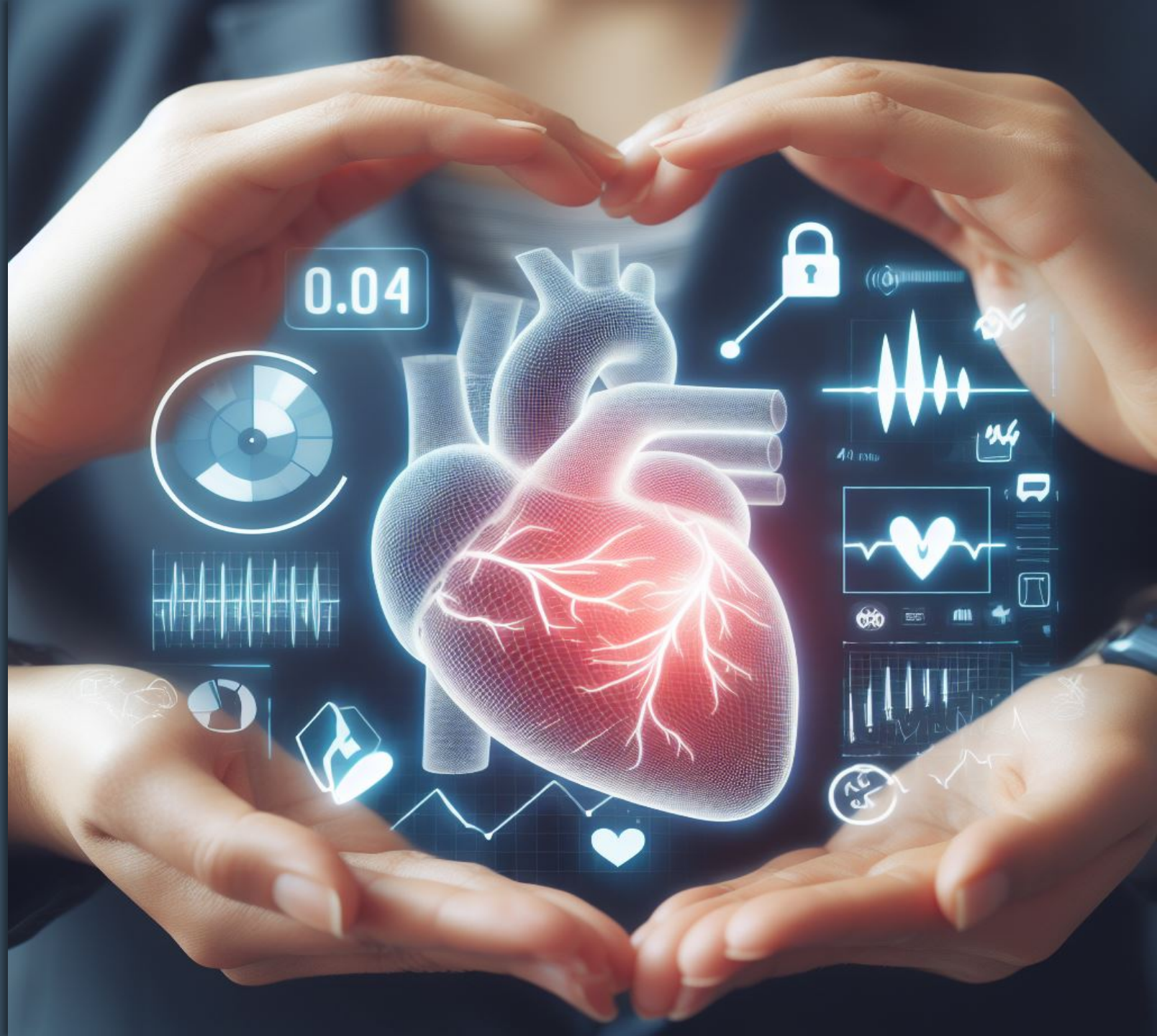
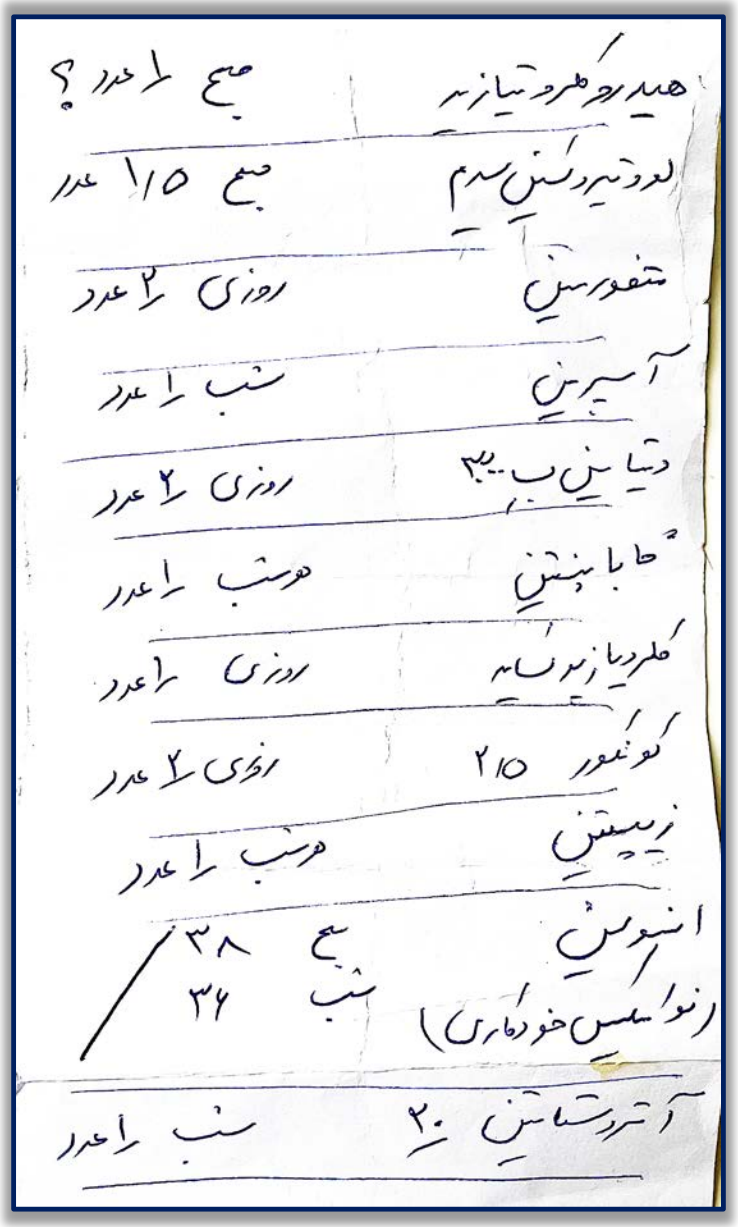
Heart Failure Management in People With Diabetes

Reza Ghanavati, MD.
Cardiovascular Specialist
Ghalb-e-Shoma Heart and Vascular Clinic



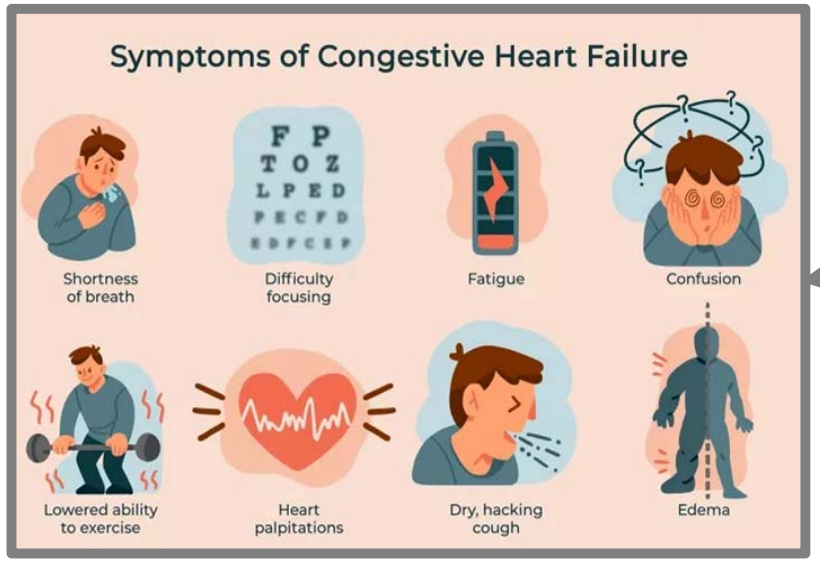
Case Vignette

- 65 y/o Lady, with DOE FC2
- **PMH**:
  - Hypothyroidism / DM for 30 years
  - HTN for 10 years
  - S/P PCI on LAD/RCA/LCX 1396
  - S/P CABG 1398
- **Ph. Exam**: unremarkable
  - BP=105/73 mmHg
  - PR=78 bpm
- **Lab test**:
  - FBS=136, HbA1c=6.4%, LDL=96, TC=165, HDL=35, TSH=3.2
- **ECG**: NSR, TWI in V1-6
- **Echo**: EF=35%, Mild MR, G1DD



DOE: Dyspnea on exertion, FC: Functional Class

Universal Definition of Heart Failure



Symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality

corroborated by *at least one* of the following

Elevated natriuretic peptide levels

or

Objective evidence of cardiogenic pulmonary or systemic congestion

	Ambulatory	Hospitalized/ decompensated
BNP, pg/ml	≥35	≥ 100
NT-proBNP, pg/ml	≥ 125	≥ 300

- Objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities such as imaging (e.g. by chest X-ray or elevated filling pressures by echocardiography) or haemodynamic measurement (e.g. right heart catheterization, pulmonary artery catheter) at rest or with provocation (e.g. exercise).

European Journal of Heart Failure (2021) 23, 352–380

Universal Definition and Classification of Heart Failure (HF)

Definition

HF is a *clinical syndrome* with current or prior

- ***Symptoms and or signs caused by a structural and/or functional cardiac***

And corroborated by at least one of the following:

- ***Elevated natriuretic peptide levels***
- ***Objective evidence of cardiogenic pulmonary or systemic congestion***

Stages

AT RISK *(STAGE A)*	**Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease**
PRE-HF *(STAGE B)*	**Patients without current or prior symptoms or signs of HF with evidence of one of the following:** • *Structural Heart Disease* • *Abnormal cardiac function* • *Elevated natriuretic peptide or cardiac troponin levels*
HF *(STAGE C)*	**Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality**
ADVANCED HF *(STAGE D)*	**Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advanced therapies transplantation, mechanical circulatory support, or palliative care**

Classification By EF

HF with reduced EF (HFrEF)
- *HF with **LVEF < 40%***

HF with mildly reduced EF (HFmrEF)
- *HF with **LVEF 41-49%***

HF with preserved EF (HFpEF)
- *HF with **LVEF > 50%***

HF with improved EF (HFimpEF)
- *HF with a baseline LVEF of < 40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF of > 40%*

Language matters! The new universal definition offers opportunities for *more precise communication* and description with terms including ***persistent HF*** instead of "stable HF," and ***HF in remission*** rather than "recovered HF."

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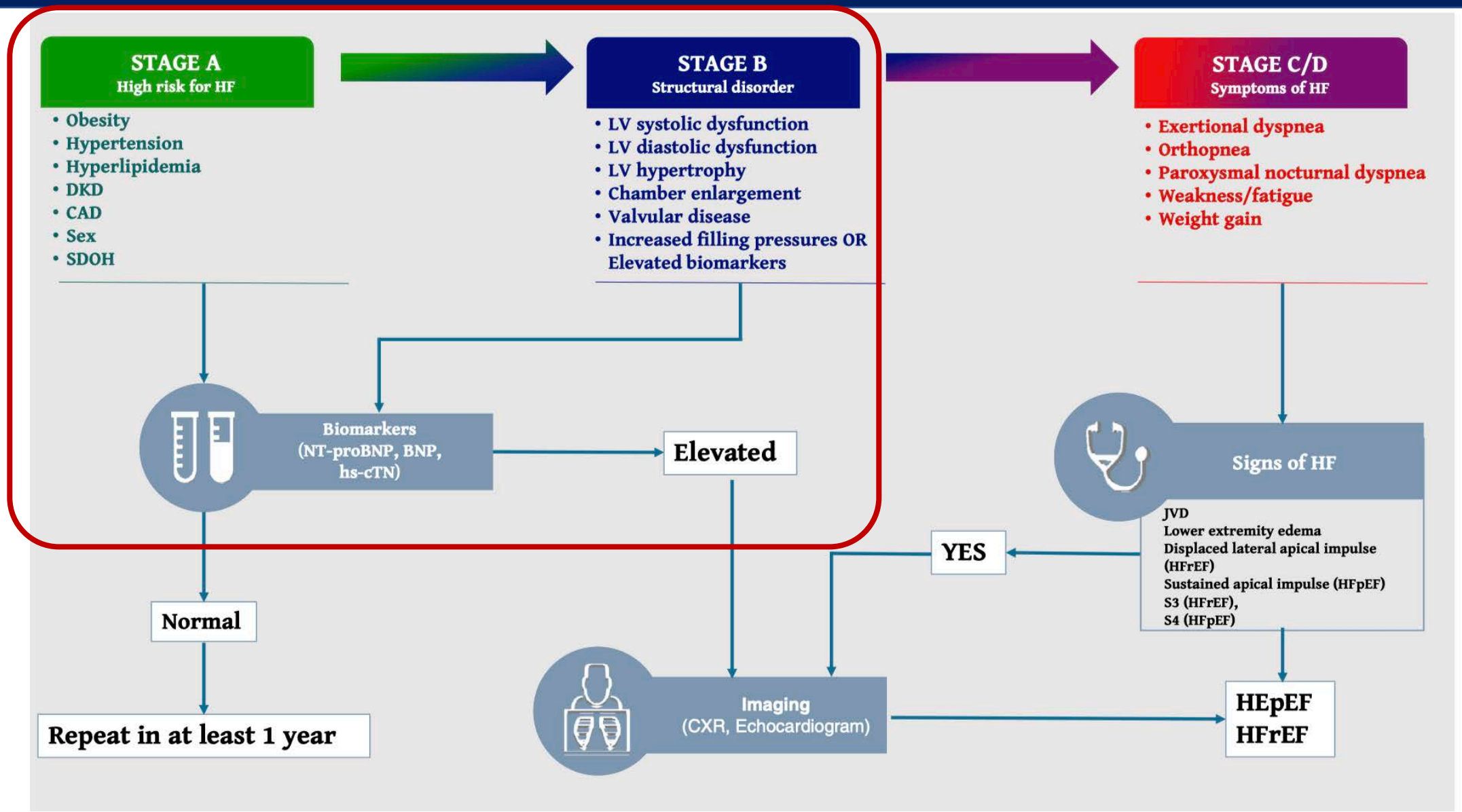
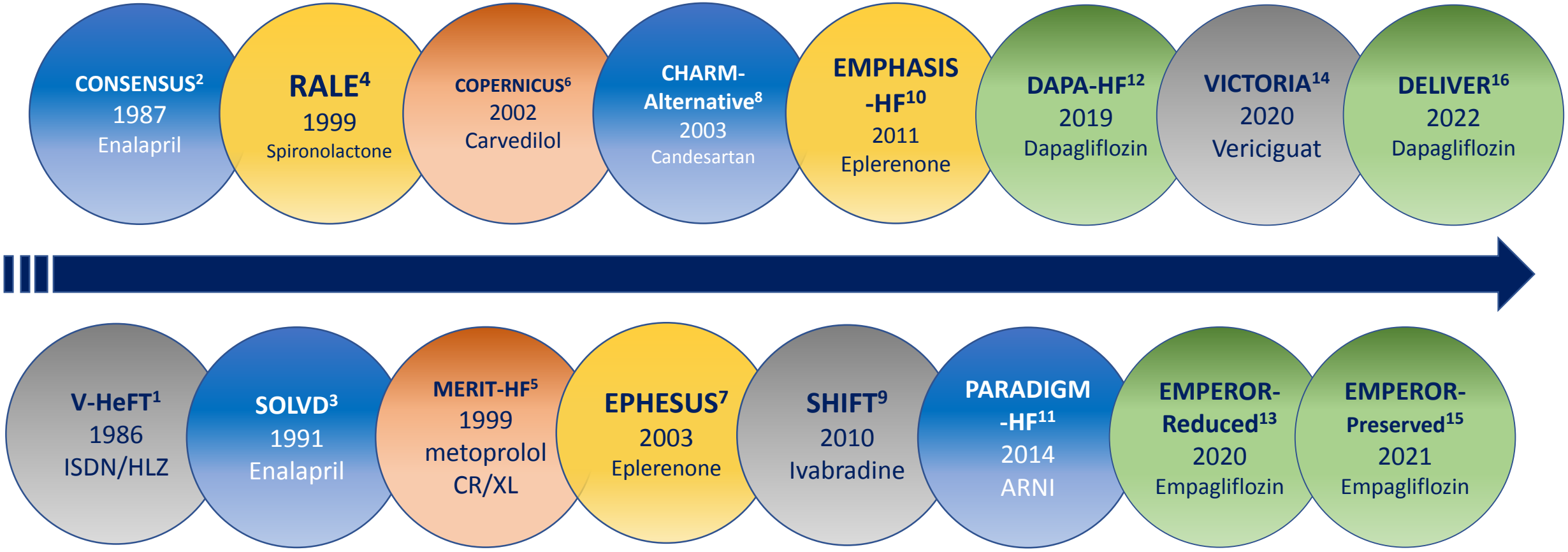
Stepwise approach for screening and diagnosis across HF stages



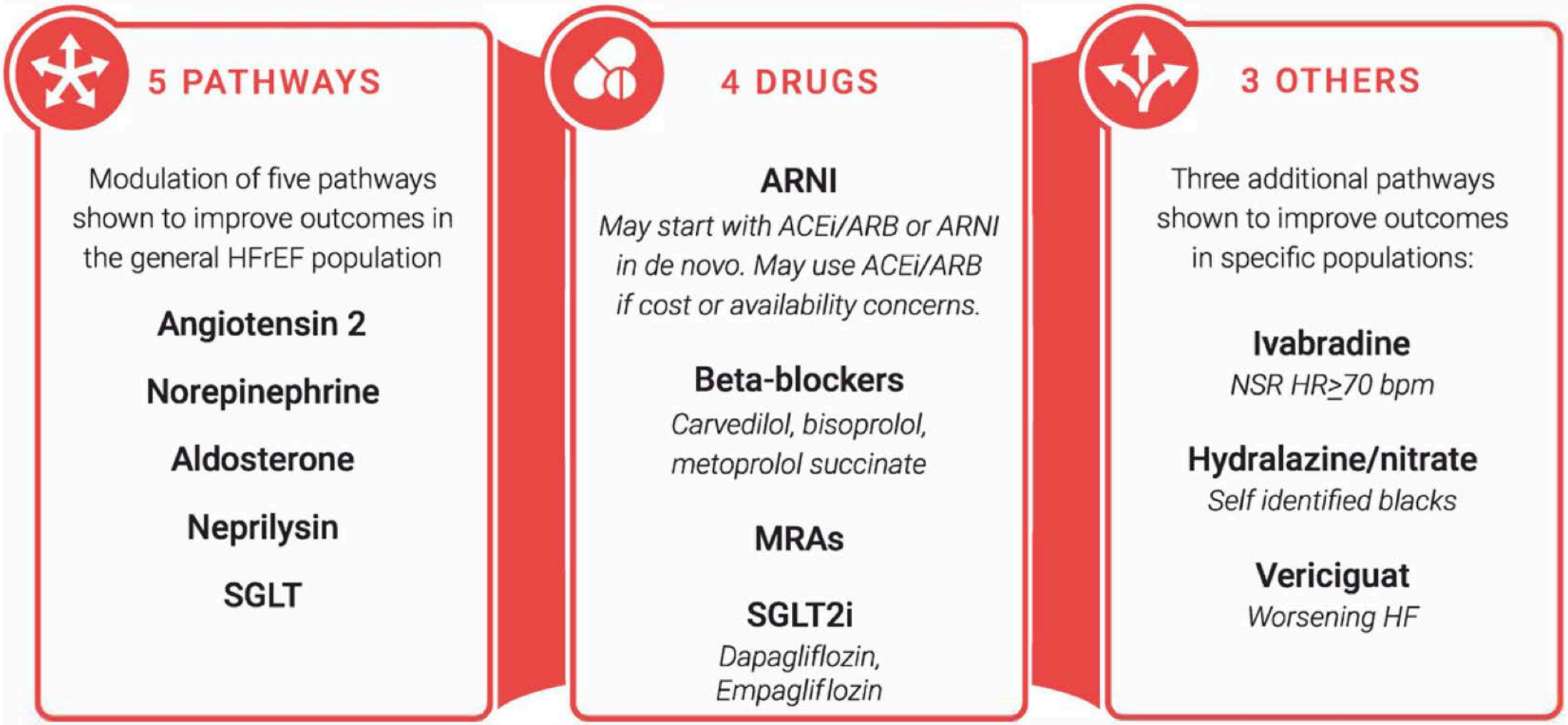
Diabetes Care 2022;45:1670–1690 | https://doi.org/10.2337/dci22-0014

Timeline of Currently Approved Comprehensive Disease-Modifying Medical Therapy (CDMMT) for Heart Failure



1- N Engl J Med 1986. 314(24):1547-52.
2- N Engl J Med 1987. 316(23):1429-35.
3- N Engl J Med 1991. 325(5):293-302.
4- N Engl J Med 1999. 341(10):709-717.
5- Lancet. 1999. 353(9169):2001-7.
6- Circulation. 2002. 106(17):2194-9.
7- N Engl J Med 2003. 348(14):1309-21.
8- Lancet. 2003. 362(9386):772-776.
9- Lancet. 2010. 376(10):875-885.
10- N Engl J Med 2011. 364(1):11-21.
11- N Engl J Med 2014. 371(11):993-1004.
12- N Engl J Med 2019; 381:1995-2008.
13- N Engl J Med 2020; 382:1883-1893.
14- N Engl J Med 2020; 383:1413-1424.
15- N Engl J Med 2021; 385:1451-1461
16- N Engl J Med 2022; 387:1089-1098

Principles and Pathophysiologic Targets of HFrEF

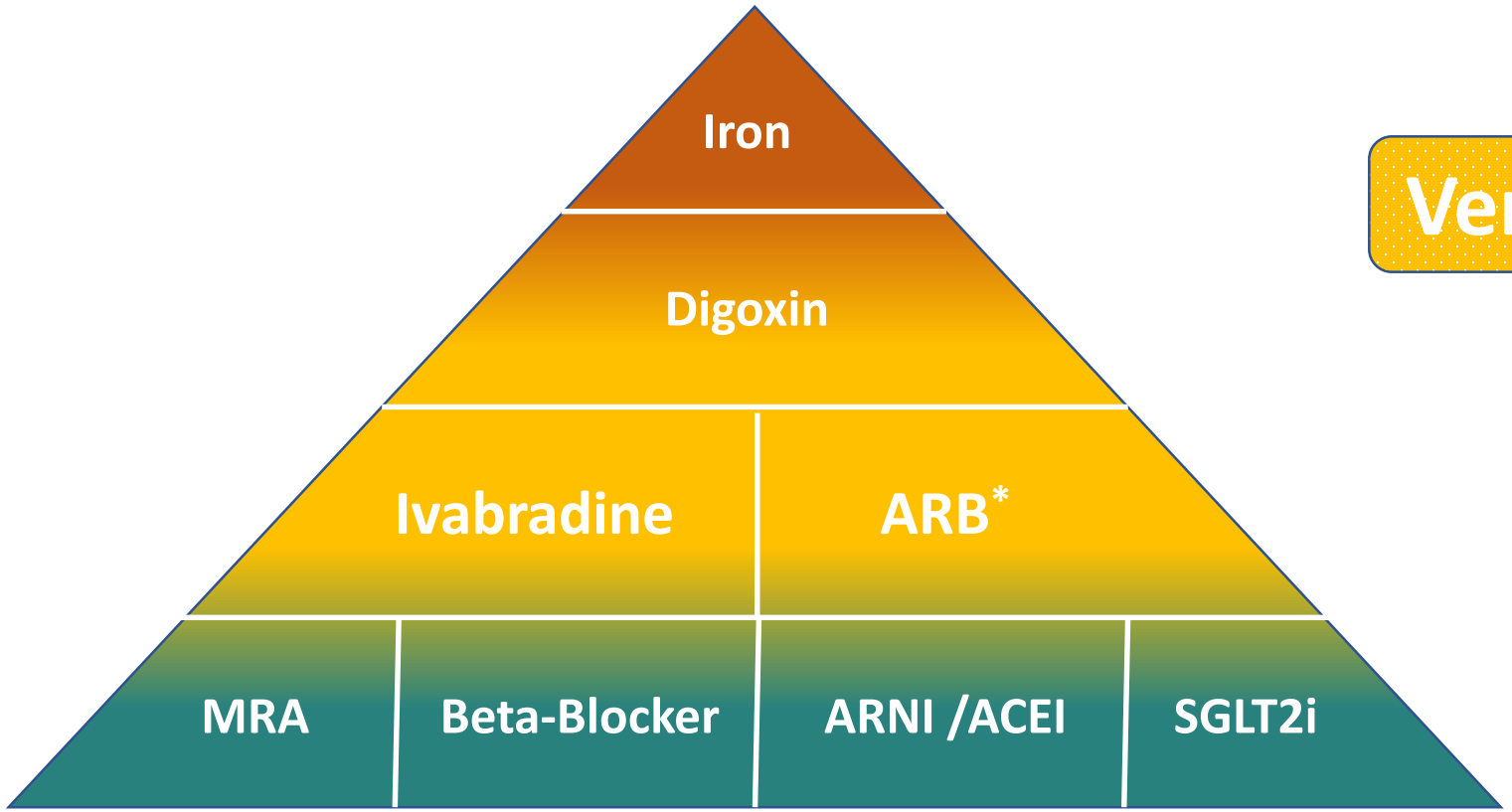


Tolerability, availability, costs, patient preference, and other consideration may impact choices, doses, and sequences of therapies – but pharmaco-pathophysiologic rationale suggests that **all attempts should be made to modulate all five pathways**.

Circulation. 2020;142:1129–1131.

Initial Guideline-Directed Medical Therapy

HFrEF Medical Treatment Pyramid



Vericigut

MRA: Mineralocorticoid Receptor Antagonist, SGLT2i: Empagliflozin/Dapagliflozin, ARB: Angiotensin receptor Blocker
* ACEI/ARNI intolerance

Starting Dose and Titration Dose

Table 3: Potential Starting Doses and Titration of Comprehensive Disease-modifying Medical Therapy

CDMMT	Starting Dose	Typical Titration Dose(s)	Final Dose	Monitoring Parameters
ACEI or ARB				
Captopril	6.25 mg three-times daily	12.5 mg three-times daily; 25 mg three-times daily	50 mg three-times daily	Monitor blood pressure, electrolytes and renal function Can titrate every 1–2 weeks in outpatients and every 1–2 days in hospitalised patients
Enalapril	2.5 mg twice daily	5 mg twice daily; 10 mg twice daily	10–20 mg twice daily	
Lisinopril	2.5–5 mg daily	10 mg daily; 20 mg daily	20–40 mg daily	
Ramipril	1.25 mg daily	2.5 mg daily; 5 mg daily	10 mg daily	
Candesartan	4-8 mg daily	16 mg daily	32 mg daily	
Losartan	25–50 mg daily	100 mg daily	150 mg daily	
Valsartan	40 mg twice daily	80 mg twice daily	160 mg twice daily	
ARNI				
Sacubitril/valsartan	24/26 mg twice daily	49/51 mg twice daily	97/103 mg twice daily	Monitoring same as ACEI or ARB Starting dose based on daily equivalent of ACEI

Card Fail Rev. 2021 Nov 26:7:e18. doi: 10.15420/cfr.2021.18

Starting Dose and Titration Dose

β-blocker				
Bisoprolol	1.25 mg daily	2.5 mg daily; 5 mg daily	10 mg daily	Initiate only in stable patients Monitor blood pressure, heart rate and for signs of congestion Can titrate every 2 weeks
Carvedilol	3.125 mg twice daily	6.25 mg twice daily; 12.5 mg twice daily	25 mg twice daily*	
Metoprolol succinate	12.5–25 mg daily	50 mg daily; 100 mg daily	200 mg daily	
MRA				
Eplerenone	25 mg daily	NA	50 mg daily	Monitor electrolytes and renal function. Avoid in eGFR ≥30 ml/min/1.73 m^2 or K^+ >5 mEq/l
Spironolactone	12.5–25 mg daily	NA	25–50 mg daily	
SGLT2i				
Dapagliflozin	10 mg daily	NA	10 mg daily	Dapagliflozin: Only if eGFR ≥30 ml/min/1.73 m^2
Empagliflozin	10 mg daily	NA	10 mg daily	Empagliflozin: Only if eGFR ≥20 ml/min/1.73 m^2

**Maximum dose of carvedilol is 50 mg twice daily for weight ≥85 kg. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; eGFR = estimated glomerular filtration rate; K+ = potassium; SGLT2i = sodium glucose cotransporter 2 inhibitor. Source: Fonarow et al. 2021*[37,39]

Card Fail Rev. 2021 Nov 26:7:e18. doi: 10.15420/cfr.2021.18

RRR and ARR in mortality and HFH

Table 2: Relative Risk Reduction in Mortality and Heart Failure Hospitalisation

CDMMT	Relative Risk Reduction in Mortality	Absolute 2-year Mortality Rate	Relative Risk Reduction in HF Hospitalisations	Absolute 2-year HF Hospitalisation Rate
None	NA	35%	NA	39%
ACEI or ARB	17%	29%	31%	27%
ARNI*	16%	24%	21%	21%
β-blocker	35%	16%	41%	13%
MRA	30%	11%	35%	8%
SGLT2i	17%	9%	30%	6%
Cumulative	**74% RRR**	**26% ARR**	**85% RRR**	**33% ARR**

**Replacing ACEI/ARB. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; ARNI = angiotensin receptor-neprilysin inhibitor; CDMMT = comprehensive disease-modifying medical therapy; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RRR = relative risk reduction; SGLT2 = sodium glucose cotransporter 2 inhibitor. Source: Fonarow et al. 2021.*[37,39]

Card Fail Rev. 2021 Nov 26:7:e18. doi: 10.15420/cfr.2021.18

The Gap

Between Evidence and Practice in Heart Failure Treatment

DAILY CARDIOLOGY ACADEMY

Real World Data

CHAMP-HF Registry

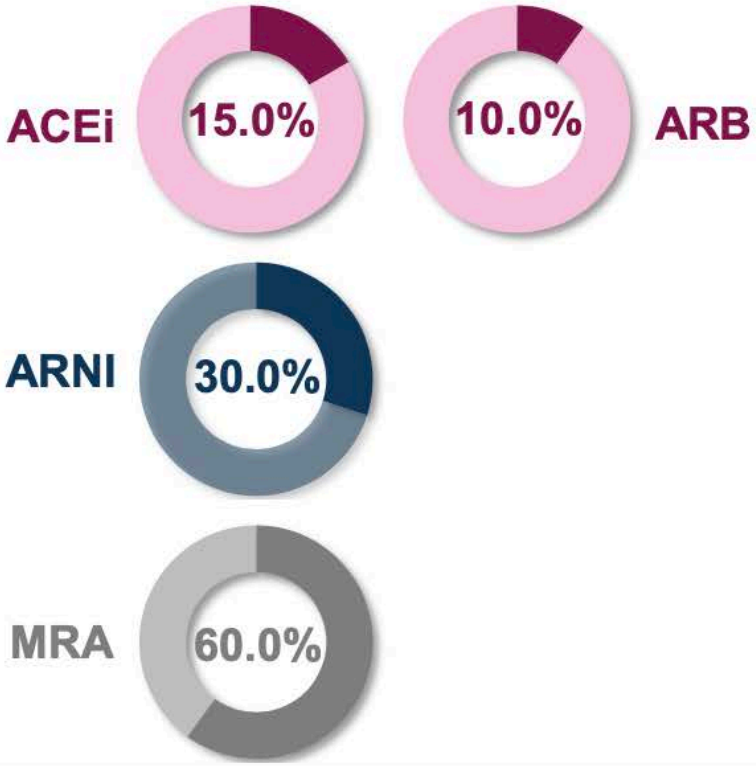
Prospective, observational study in US outpatients with chronic HFrEF (N=2588) to evaluate the degree of titration of HFrEF GDMT (2015-2017)[1]

Patients Achieving Target Doses at 1 Year

Savarese et al

Observational cohort study using data from healthcare databases in Sweden, UK, and US to identify patients (N=68,172) with new initiation of GDMT following recent hHF[a] (2016-2019)[2]

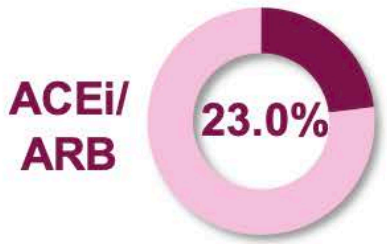
Patients Achieving Target Doses at 1 Year



BIOSTAT-CHF

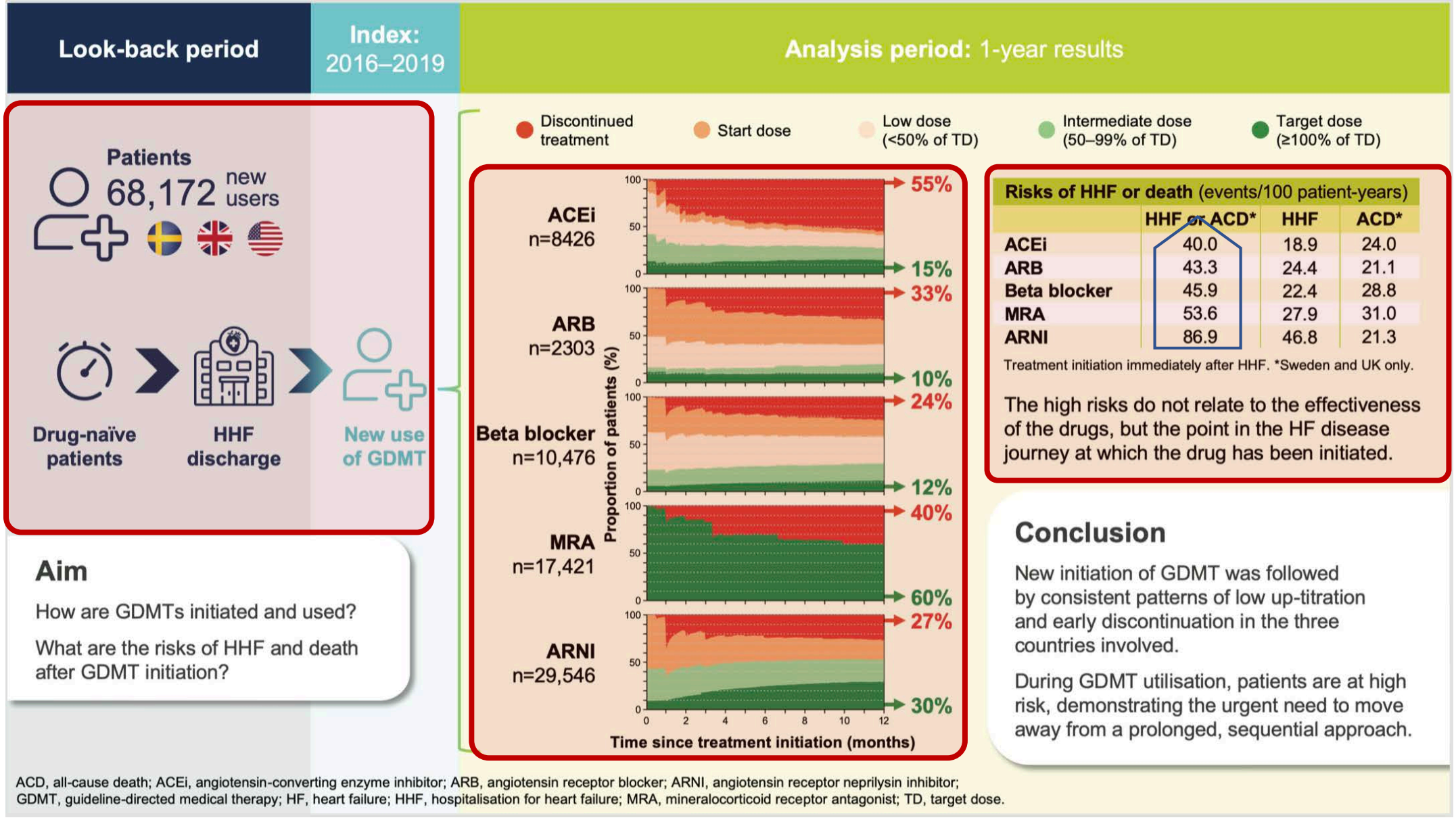
Multicenter, prospective, observational study in patients with HFrEF (N=2100) who were not previously on ACEi/ARB or receiving ≤50% of the target dose from 11 European countries (2010-2014)[3,4]

Patients Achieving Target Doses at 9 Months



1. Greene SJ et al. *J Am Coll Cardiol*. 2019;73;2365-2383; 2. Savarese G et al. Online ahead of print. *Eur J Heart Fail*. 2021; 3. Voors AA et al. *Eur J Heart Fail*. 2016;18:716-726; 4. Kobayashi M et al. *Clin Cardiol*. 2021;44:780-788.

Real World Data



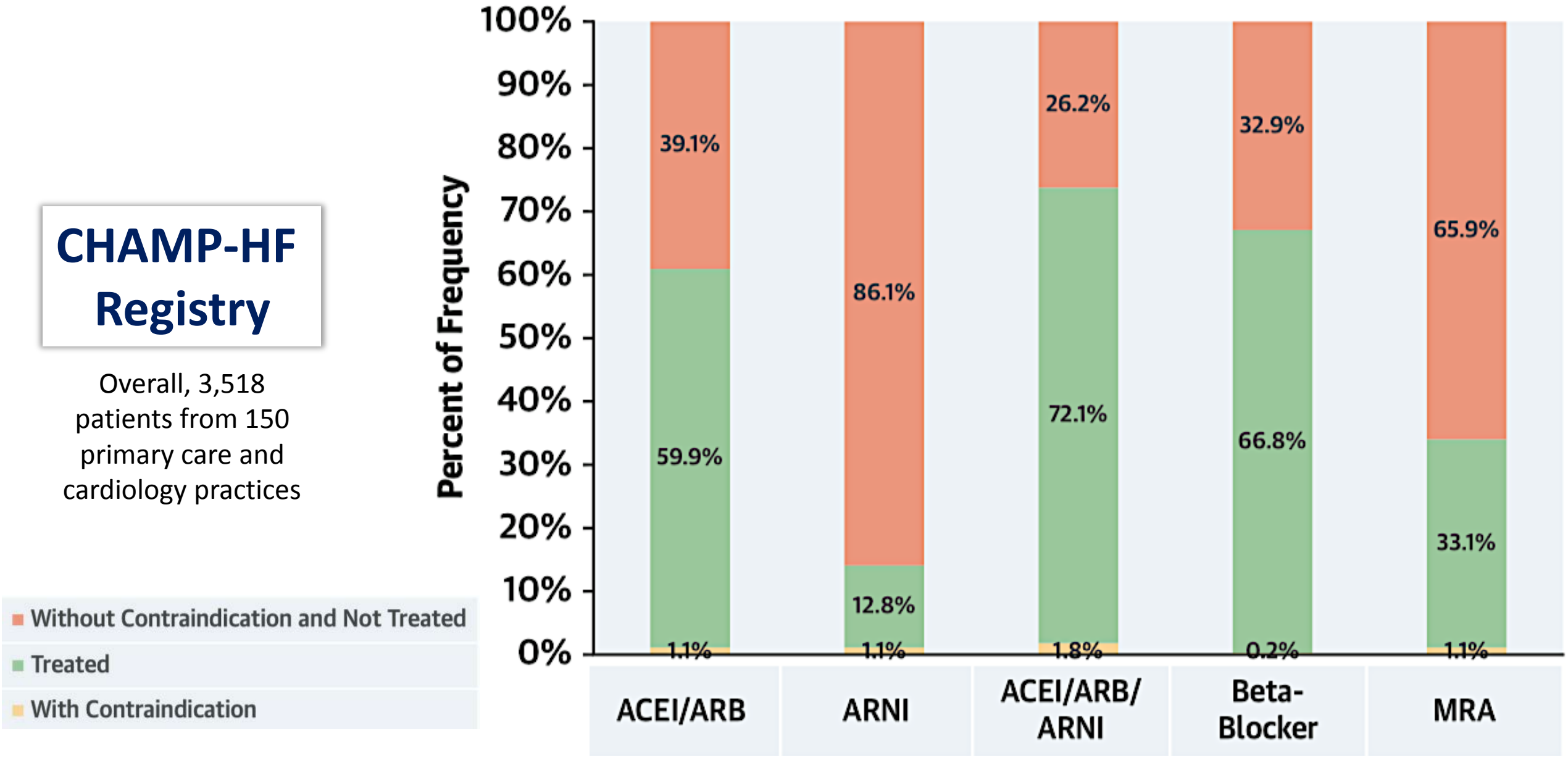
ACD, all-cause death; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; HHF, hospitalisation for heart failure; MRA, mineralocorticoid receptor antagonist; TD, target dose.

European Journal of Heart Failure (2021) 23, 1499–1511

Use of Guideline-Directed Medical Therapy Among Patients With HFrEF in Contemporary U.S. Outpatient Practice

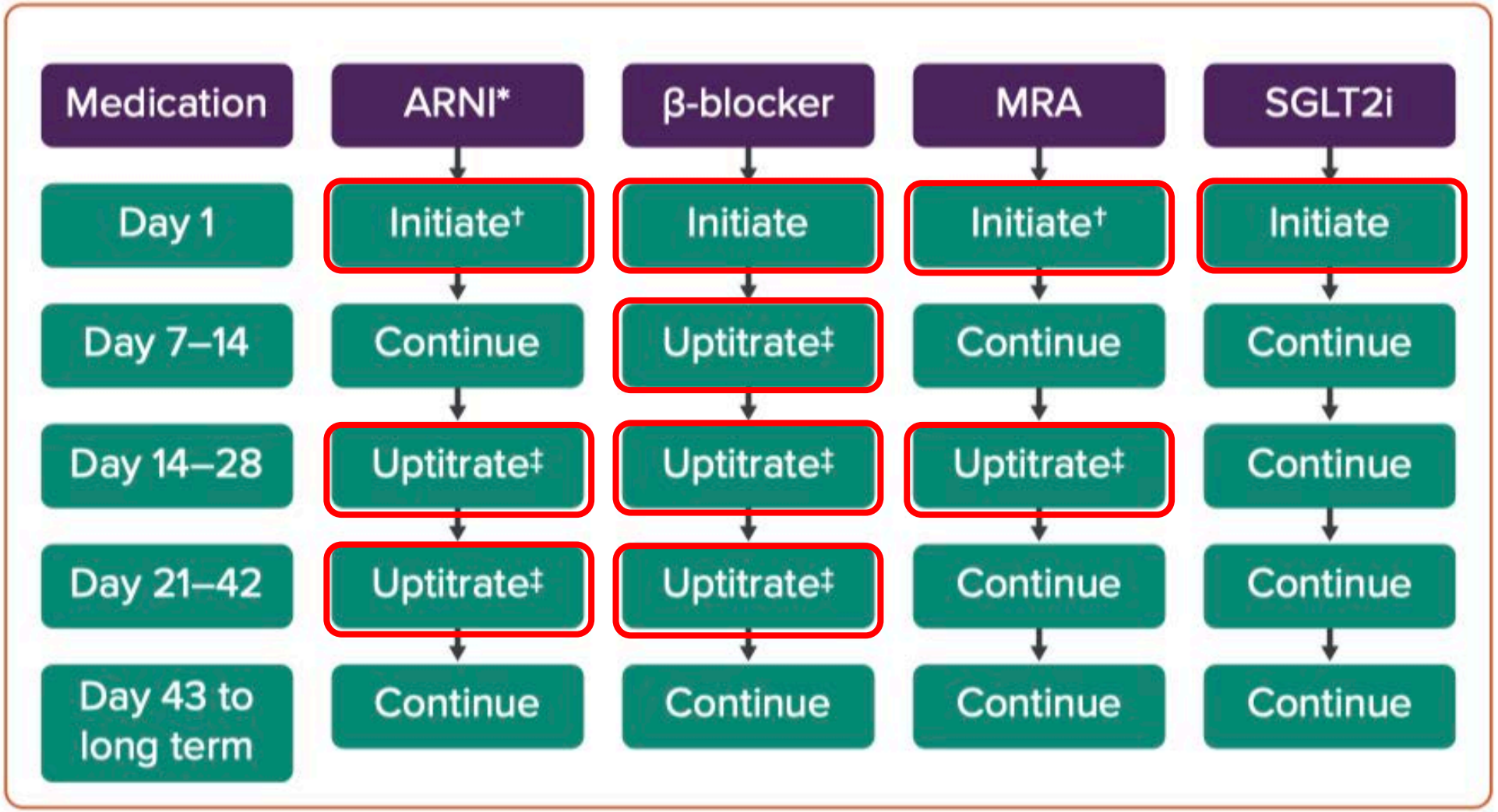
CHAMP-HF Registry

Overall, 3,518 patients from 150 primary care and cardiology practices



Greene, S.J. et al. J Am Coll Cardiol. 2018;72(4):351–66.

Rapid Sequence Initiation of Quadruple Medical Therapy

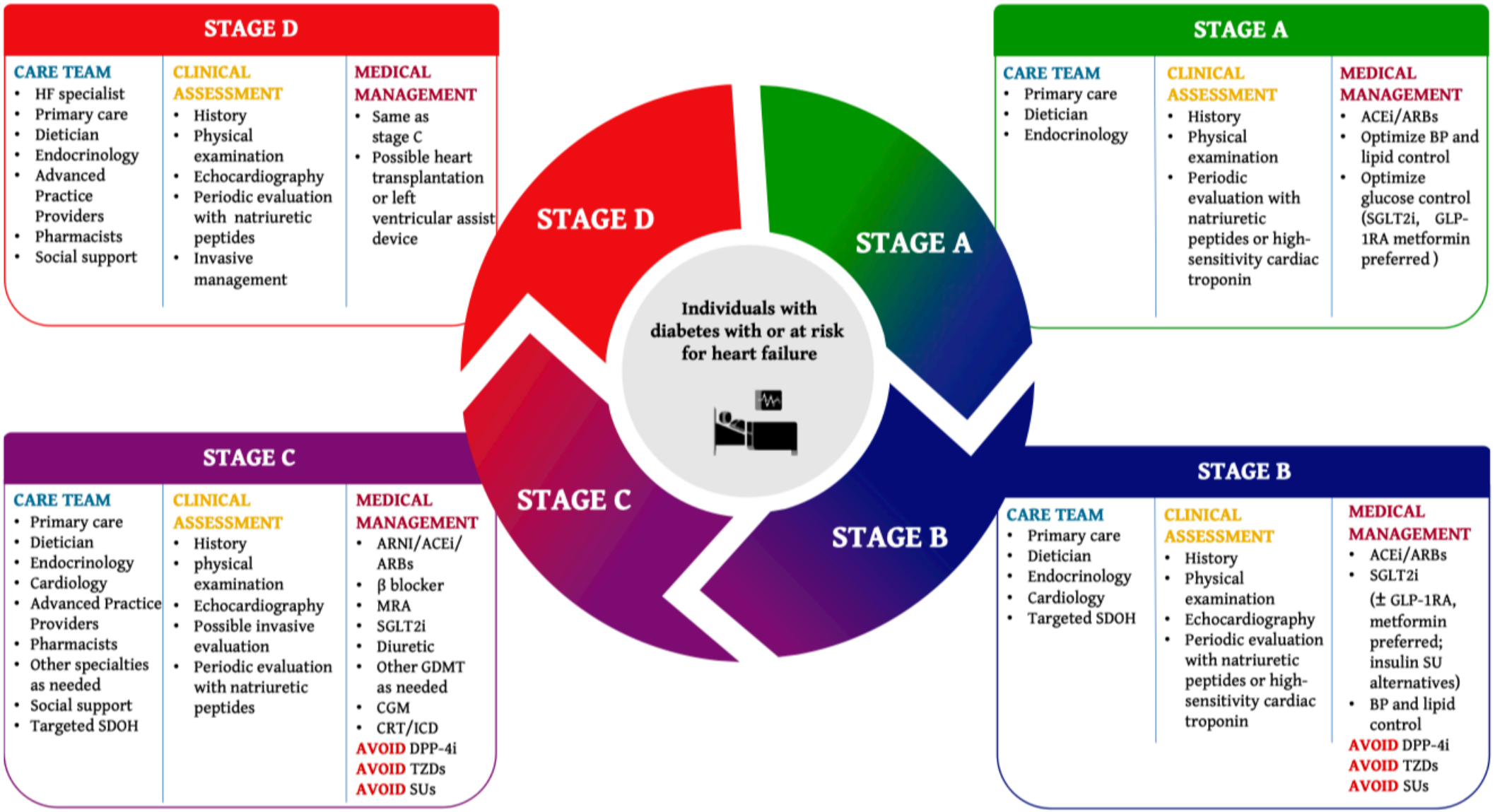


Starting doses for medications:
ARNI (sacubitril/valsartan 24/26 mg twice daily.
β-blocker bisoprolol 1.25 mg daily; carvedilol 3.125 mg twice daily; metroprolol succinate 12.5–25 mg daily.
MRA (eplerenone 25 mg daily; spironolactone 12.5–25 mg daily).
SGLT2i (dapagliflozin 10 mg daily; empagliflozin 10 mg daily).

Data were obtained from the COPERNICUS, EMPHASIS-HF, PIONEER-HF, and EMPEROR-Reduced trials. **Low starting doses should be used, with β-blocker up-titration prioritized**. **Clinical benefits of all medications are apparent within 30 days of initiation**. This strategy could be tested in randomized clinical trials, but available evidence suggests the benefits of this strategy outweigh the risks.

Greene, J. Stephen. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure— Optimizing Therapy With the Need for Speed, JAMA Cardiol. 2021 Jul 1;6(7):743-744.

Multidisciplinary personalized care in individuals with HF and diabetes

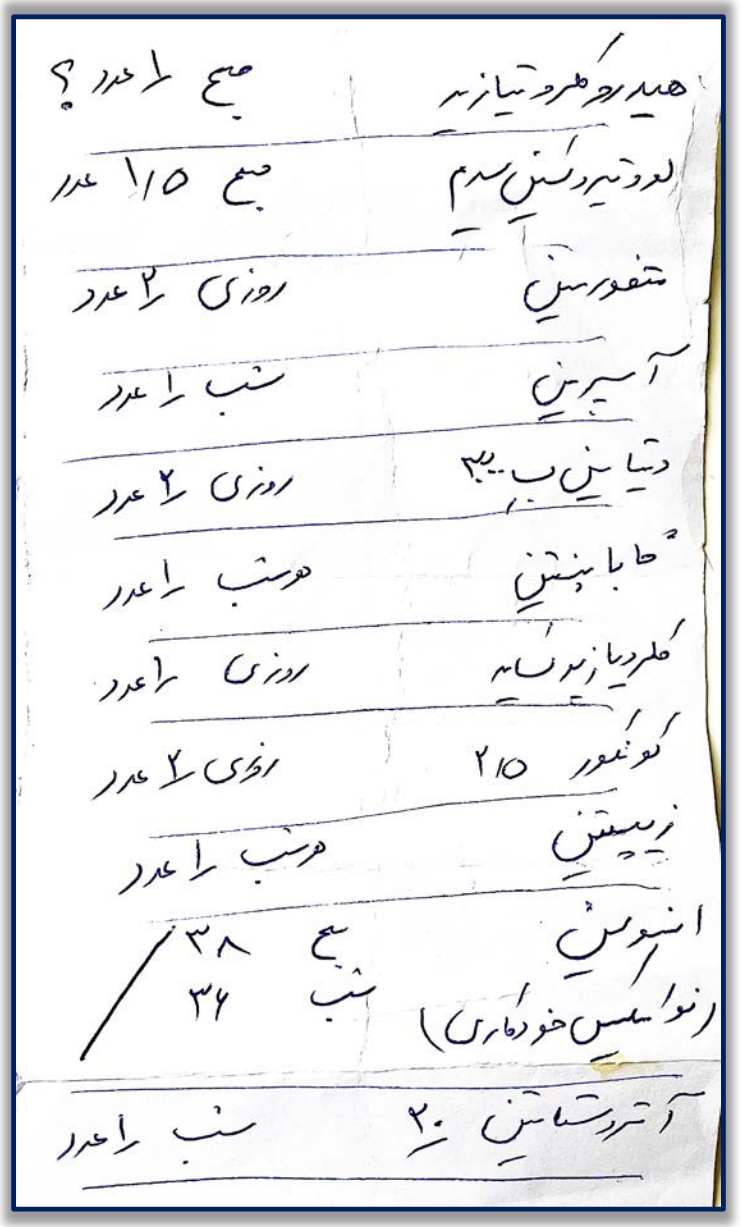


Diabetes Care 2022;45:1670–1690 | https://doi.org/10.2337/dci22-0014

Case Vignette

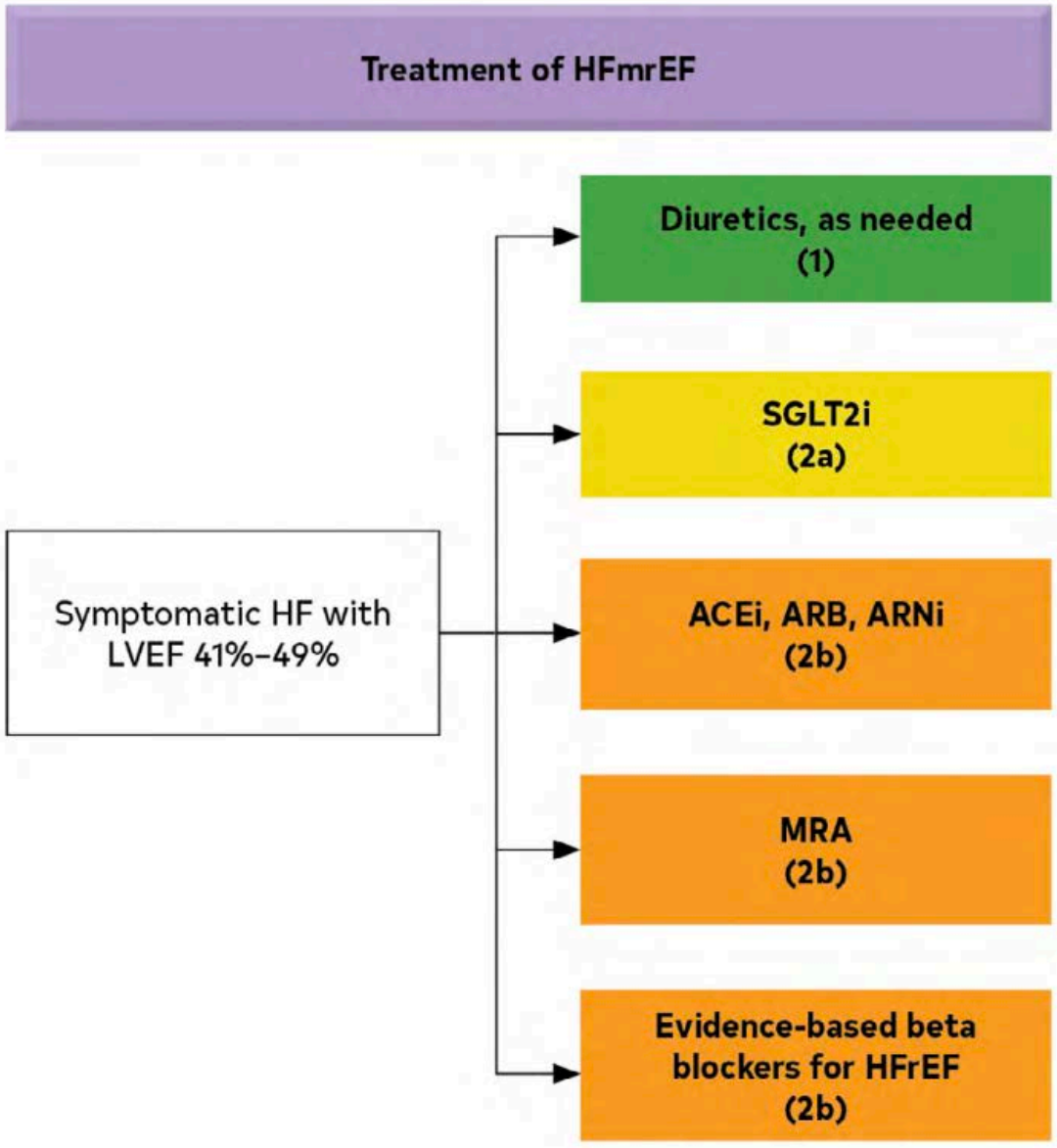
- ASA 80 Daily
- Atorvastatin 40mg Daily
- Bisoprolol 10mg Daily
- Sacubitril/Valsartan 50(24/26) mg BID
- Eplerenone 25mg Daily
- Empagliflozin 10mg Daily

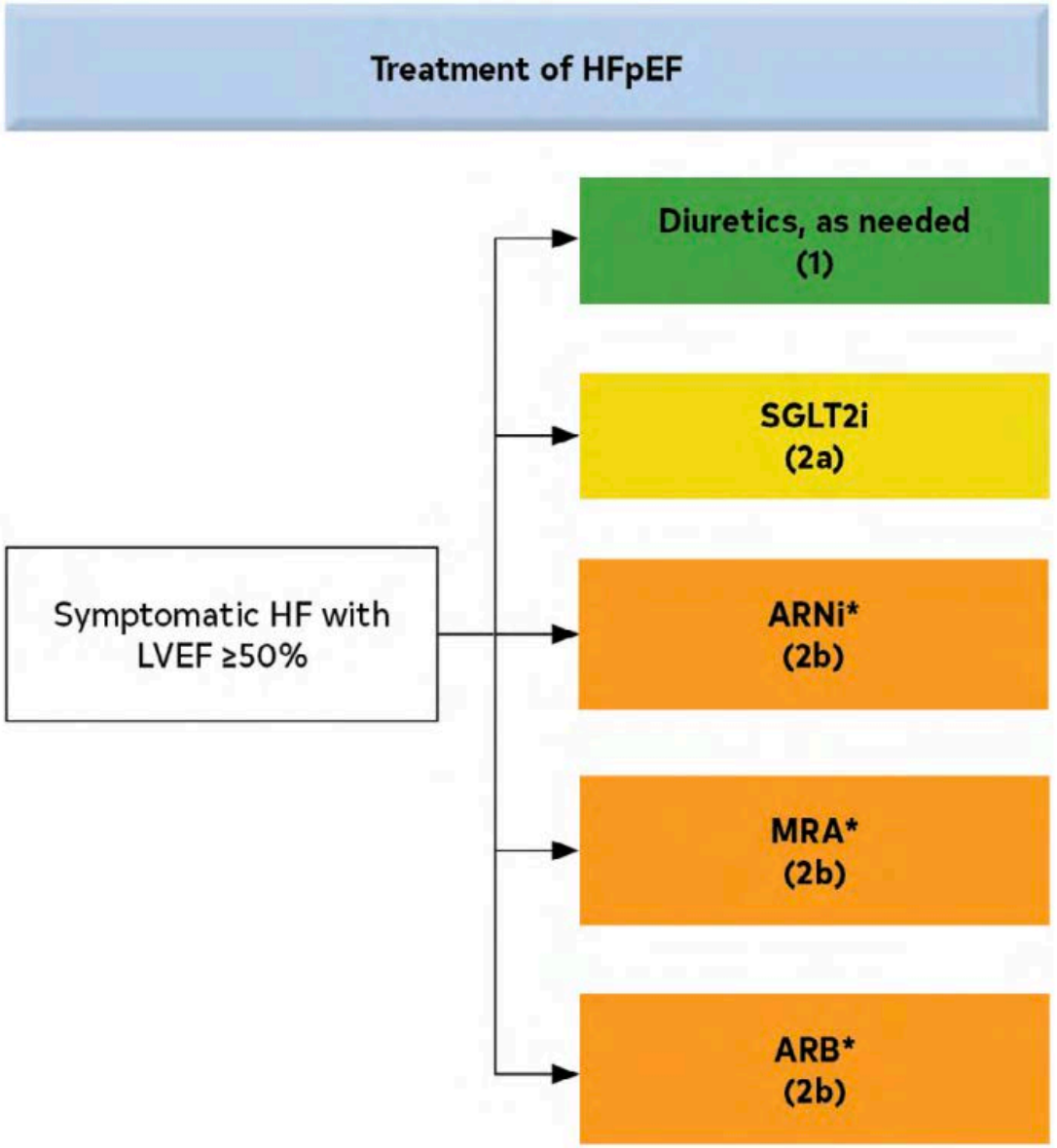
Endocrinologist consult



DOE: Dyspnea on exertion, FC: Functional Class

HFmrEF & HFpEF





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