New Paradigms in Heart Failure: a Preventable and Treatable Disease

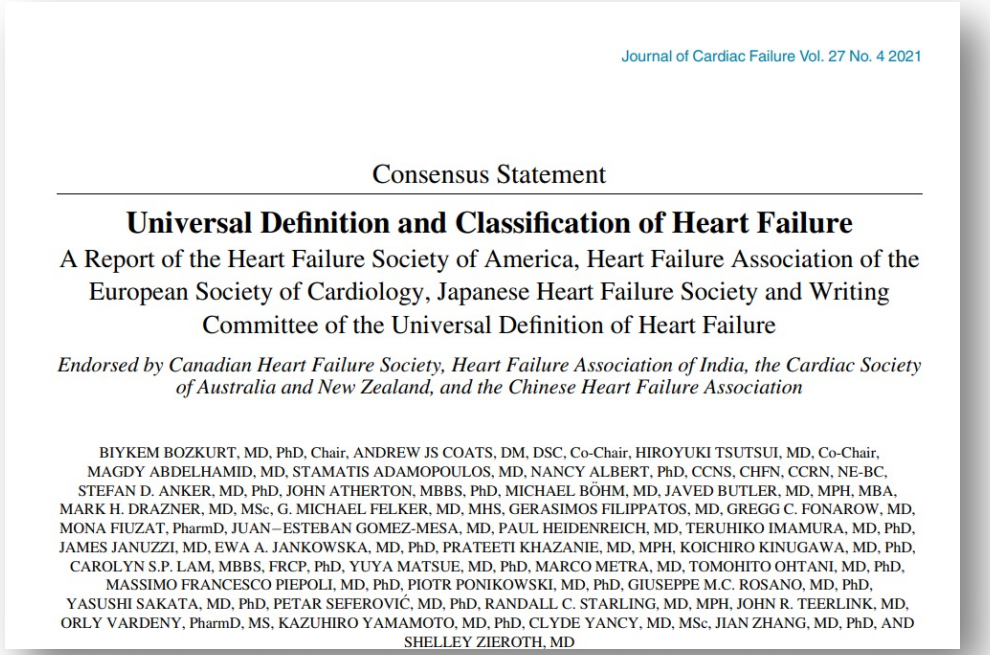
Biykem Bozkurt, MD PhD, FHFSA, FACC, FAHA, FESC
The Mary and Gordon Cain Chair & Professor of Medicine
Associate Provost of Faculty Affairs
Senior Associate Dean for Faculty Development
Director, Winters Center for HF Research, Associate Director, Cardiovascular Research Institute
Baylor College of Medicine, Houston, TX
Medicine Chief, Michael E. DeBakey VA Medical Center
Editor-in-Chief, *JACC: Heart Failure*
@BiykemB

Baylor College of Medicine

Disclosures

- **Clinical Event Committee**: Abbott, GUIDE HF Trial
- **Consultation:** Astra Zeneca, Amgen, Bristol Myers Squibb, scPharmaceuticals, Baxter, Sanofi-Aventis, Relypsa, Vifor, Boehringer Ingelheim
- **DSMC:** Anthem Trial, Liva Nova

Universal Definition of HF (UDHF)



Journal of Cardiac Failure Vol. 27 No. 4 2021

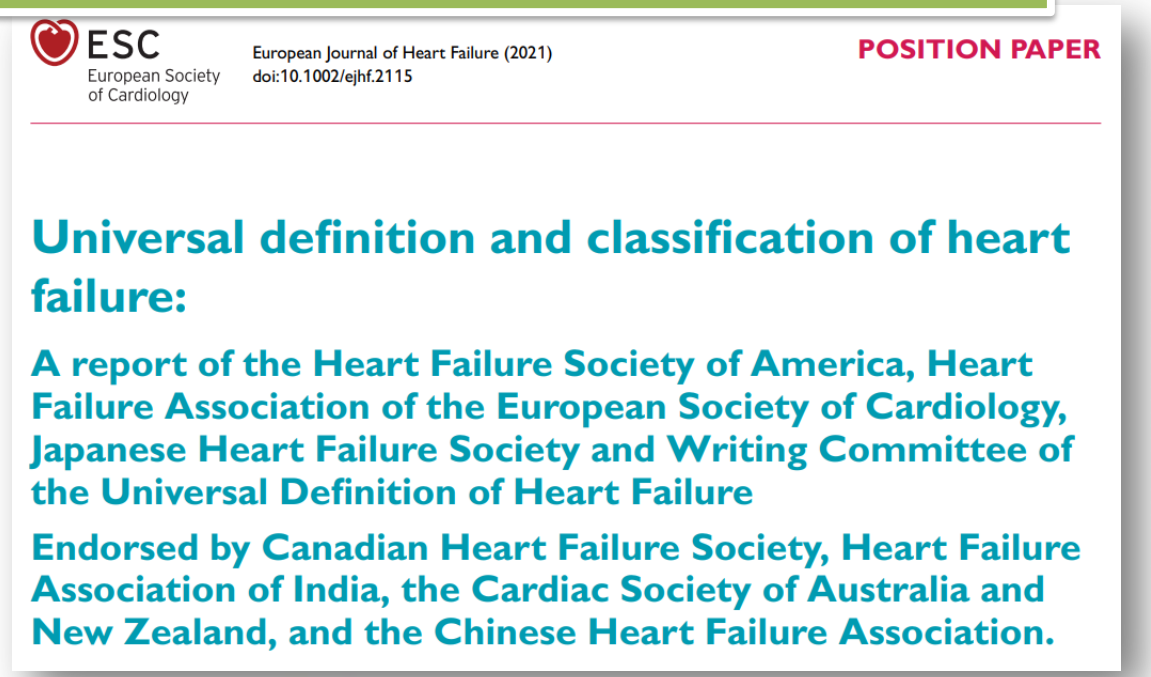
Consensus Statement

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association

BIYKEM BOZKURT, MD, PhD, Chair, ANDREW JS COATS, DM, DSC, Co-Chair, HIROYUKI TSUTSUI, MD, Co-Chair, MAGDY ABDELHAMID, MD, STAMATIS ADAMOPOULOS, MD, NANCY ALBERT, PhD, CCNS, CHFN, CCRN, NE-BC, STEFAN D. ANKER, MD, PhD, JOHN ATHERTON, MBBS, PhD, MICHAEL BÖHM, MD, JAVED BUTLER, MD, MPH, MBA, MARK H. DRAZNER, MD, MSc, G. MICHAEL FELKER, MD, MHS, GERASIMOS FILIPPATOS, MD, GREGG C. FONAROW, MD, MONA FIUZAT, PharmD, JUAN–ESTEBAN GOMEZ-MESA, MD, PAUL HEIDENREICH, MD, TERUHIKO IMAMURA, MD, PhD, JAMES JANUZZI, MD, EWA A. JANKOWSKA, MD, PhD, PRATEETI KHAZANIE, MD, MPH, KOICHIRO KINUGAWA, MD, PhD, CAROLYN S.P. LAM, MBBS, FRCP, PhD, YUYA MATSUE, MD, PhD, MARCO METRA, MD, TOMOHITO OHTANI, MD, PhD, MASSIMO FRANCESCO PIEPOLI, MD, PhD, PIOTR PONIKOWSKI, MD, PhD, GIUSEPPE M.C. ROSANO, MD, PhD, YASUSHI SAKATA, MD, PhD, PETAR SEFEROVIĆ, MD, PhD, RANDALL C. STARLING, MD, MPH, JOHN R. TEERLINK, MD, ORLY VARDENY, PharmD, MS, KAZUHIRO YAMAMOTO, MD, PhD, CLYDE YANCY, MD, MSc, JIAN ZHANG, MD, PhD, AND SHELLEY ZIEROTH, MD



ESC European Society of Cardiology

European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2115

POSITION PAPER

Universal definition and classification of heart failure:

A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association.

HFSA
HEART FAILURE SOCIETY OF AMERICA

HFA
Heart Failure
Association

The Japanese
Heart Failure Society

CHFS/SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardia

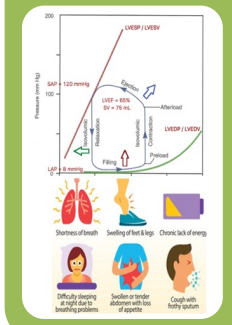
HEART FAILURE ASSOCIATION OF INDIA

CSANZ
Cardiac Society of Australia and New Zealand

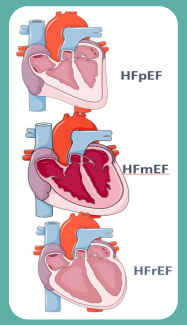
Chinese Heart Failure Association

Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021

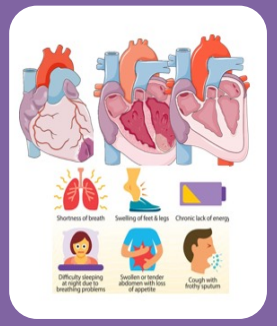
Existing Definitions and Classifications



Overarching definition



EF Phenotype



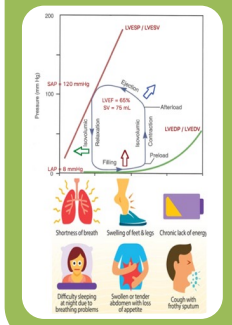
Stages

Syndrome dx, Trials, Research

Successful GDMT

Initially to Emphasize Prevention

Definition of the Syndrome



Overarching definition

Former Definitions of Heart Failure

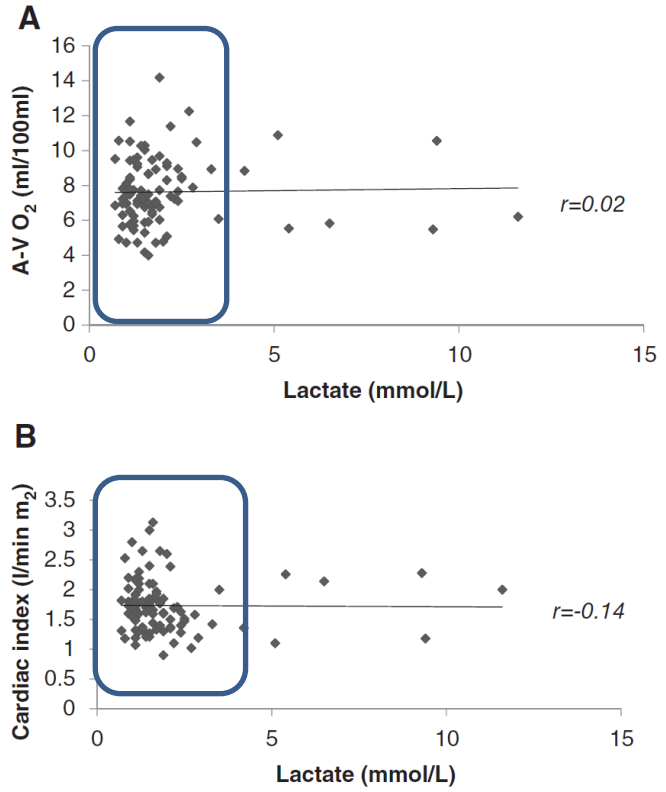
"Textbook" definition :

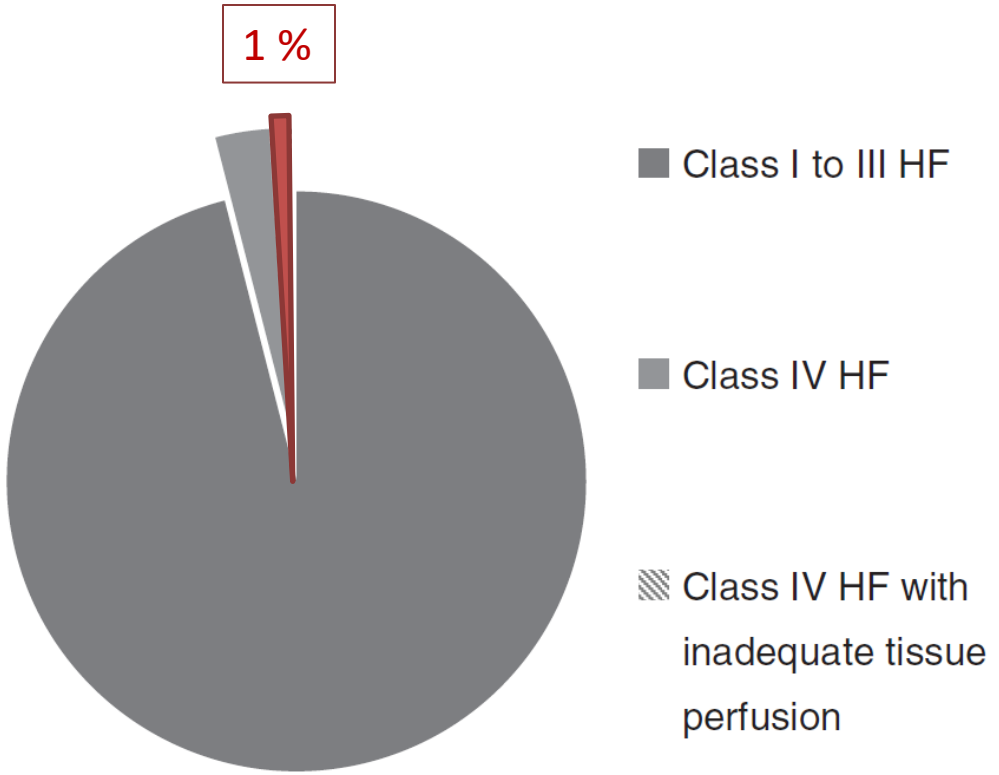
"A clinical syndrome caused by the inability of the heart to meet tissue metabolic requirements"

Few HF Patients Meet the Historical HF Definition:

Heart failure is a condition in which the heart can't pump enough blood to meet the body's needs.

Circa 1977: "Abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues"





Wagner S, Cohn K. Heart failure. A proposed definition and classification. Arch Intern Med 1977;137:675–678.

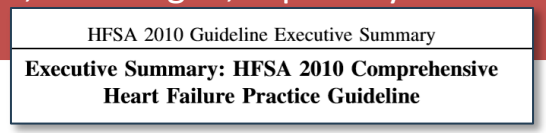
Braunwald E. Heart failure. JACC Heart Fail 2013;1:1–20

Francis GS, Wilson Tang WH, Walsh RA. Pathophysiology of heart failure. In: Fuster V, Walsh RA, Harrington RA, eds. Hurst's The Heart, 13th ed; 2011.pp719–738

Adamo L, Nassif ME, Novak E, LaRue SJ, Mann DL. Prevalence of lactic acidemia in patients with advanced heart failure and depressed cardiac output. Eur J Heart Fail. 2017;19(8):1027-1033

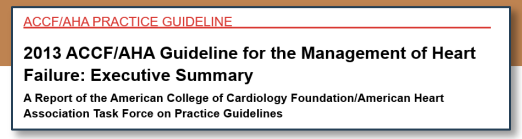
HF Definition in Guidelines Differed

HF is a syndrome caused by **cardiac dysfunction**, generally resulting from myocardial muscle dysfunction or loss and characterized by either LV dilation or hypertrophy or both. Whether the dysfunction is primarily systolic or diastolic or mixed, it leads to **neuro-hormonal and circulatory abnormalities, usually resulting in characteristic symptoms** such as fluid retention, shortness of breath, and fatigue, especially on exertion.


HFSA 2010 Guideline Executive Summary

Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

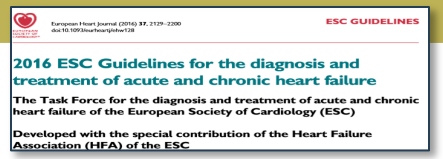
HF is a complex **clinical syndrome** that results from any structural or functional impairment of **ventricular filling or ejection of blood**


ACCF/AHA PRACTICE GUIDELINE

2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

HF is a **clinical syndrome** characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, **resulting in a reduced cardiac output and/or elevated intracardiac pressures** at rest or during stress.

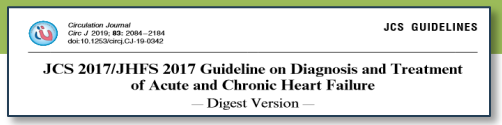

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

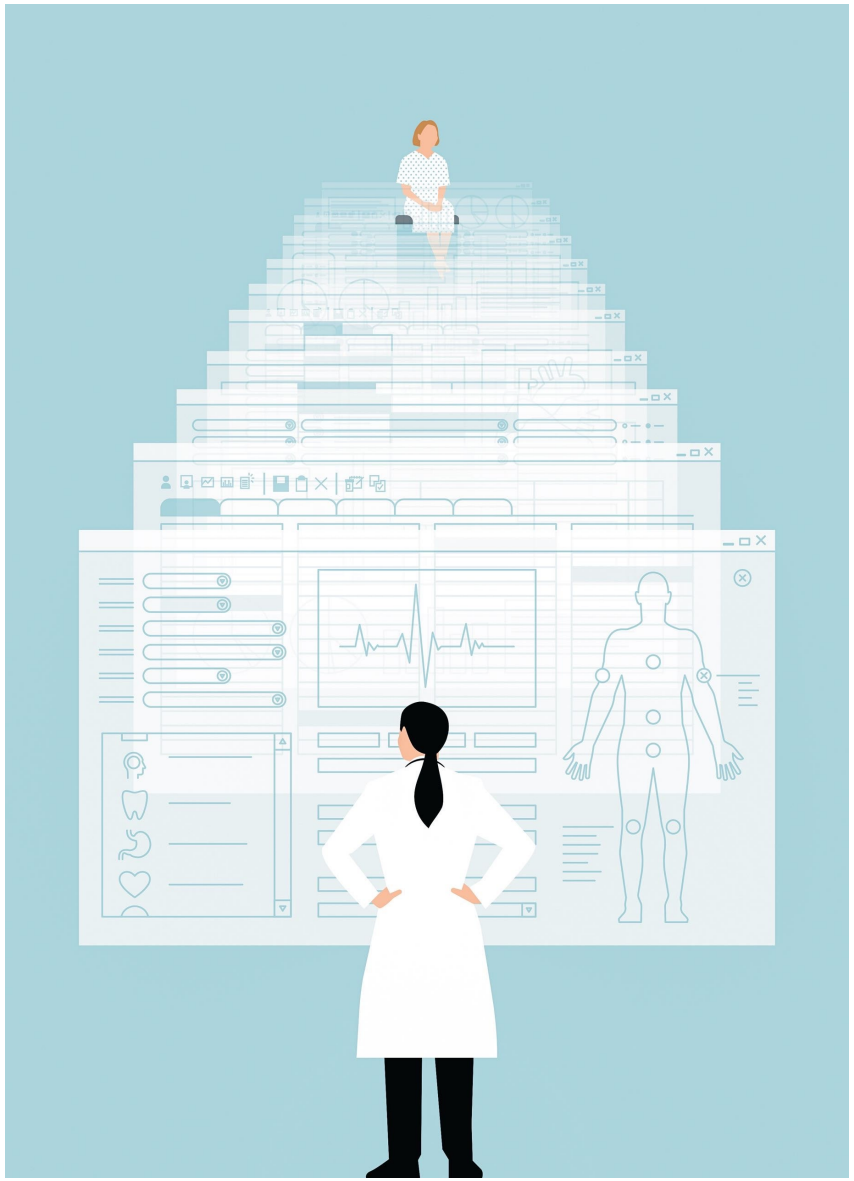
Heart failure is defined as a **clinical syndrome** consisting of dyspnea, malaise, swelling and/or decreased exercise capacity **due to the loss of compensation for cardiac pumping function** due to structural and/or functional abnormalities of the heart


JCS GUIDELINES

JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure

— Digest Version —

Chaos in Documentation/Administrative Coding



Stage A

Stage B

Stage C/ D

At-risk for HF

CMP

Stage C/D

ICD-10-HF I50: Coding guidance states first code following

- HF complicating abortion or ectopic pregnancy
- HF due to hypertension (I11.0);
- HF due to hypertension with CKD (I13.-);
- rheumatic heart failure (I09.81)
- HF following surgery
- I50.2: Systolic (congestive) heart failure
- I50.4 Combined systolic (congestive) and diastolic (congestive) heart failure

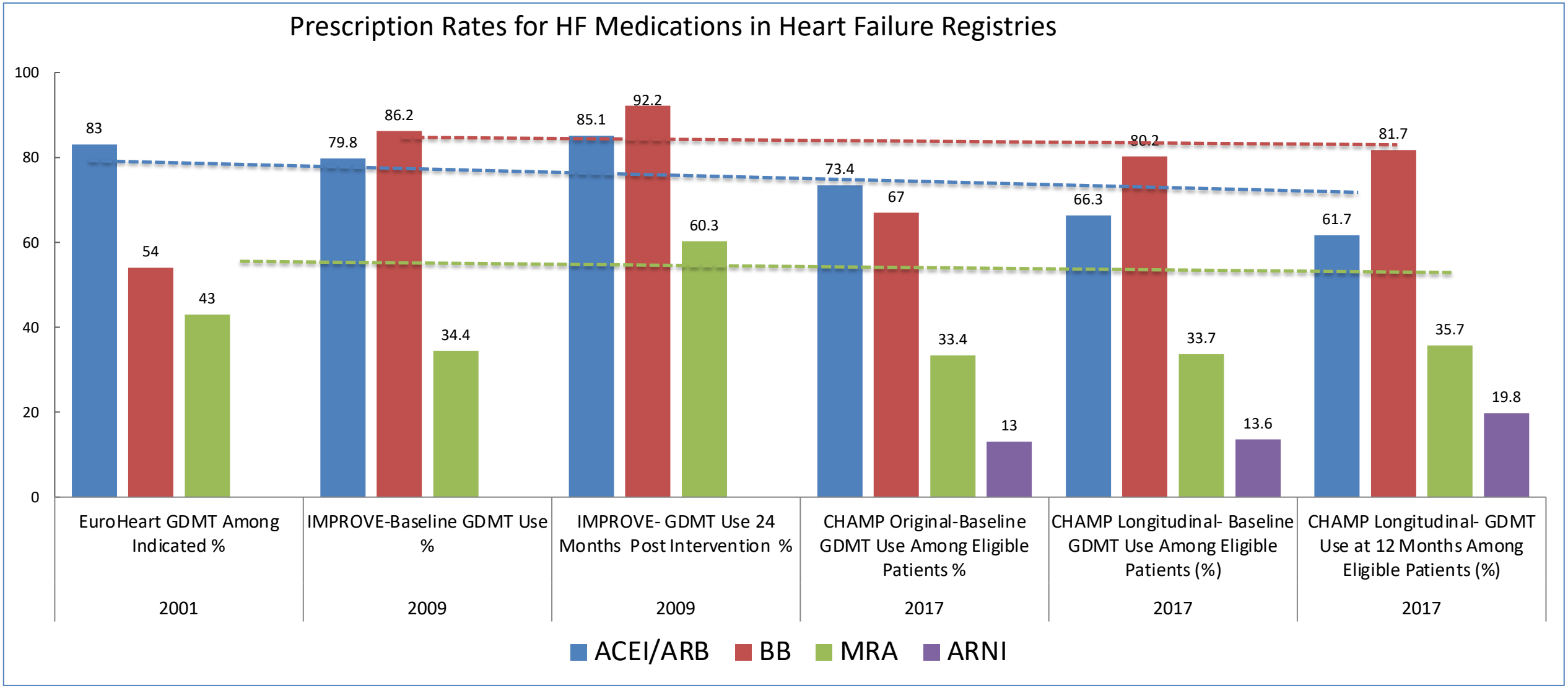
ICD-10-CMP I42.9:

- Cardiomyopathy (familial) (idiopathic) I42.9
- secondary I42.9
- idiopathic I42.9
- primary (idiopathic) I42.9
- Myocardiopathy (congestive) (constrictive) (familial) (hypertrophic nonobstructive) (idiopathic) (infiltrative) (obstructive) (restrictive) (sporadic) I42.9

No code for at-risk for HF or pre-HF

- to capture Stage A /at-risk / preHF prevalence
- to treat for specific risk

Failure: Treatment of HF in the Last 2 Decades



Bozkurt B. J Am Coll Cardiol. 2019 May 21;73(19):2384-2387

Other Disease Definitions with Objective Quantitative Markers

Hypertension

- BP consistently higher than 130/80

Diabetes

- Fasting glucose ≥126 mg/dL or non-fasting ≥200 mg/dL or Hb A1c ≥6.5%

CKD

- eGFR <60 ml/min/1.73m^2 on at least 2 occasions 90 days apart

COPD

- GOLD grades by FEV1 % predicted thresholds

Osteoporosis:

- BMD ≥2.5 SD below the normal mean for young-adult women

Components of a HF Definition

1

Symptoms and Signs

Comorbidities: CKD, Obesity, Volume Overload, Atrial Fibrillation, OSA, Lung Disease

↓ **Specificity**

Components of a HF Definition

2

Cardiac Structural and Functional Abnormality

Ischemic Heart Disease, Cardiomyopathy without Symptoms

Stage B

Components of a HF Definition

3

Elevated Filling Pressures

Natriuretic Peptides

Age, CKD, Sex, Obesity, Atrial Fibrillation, Other

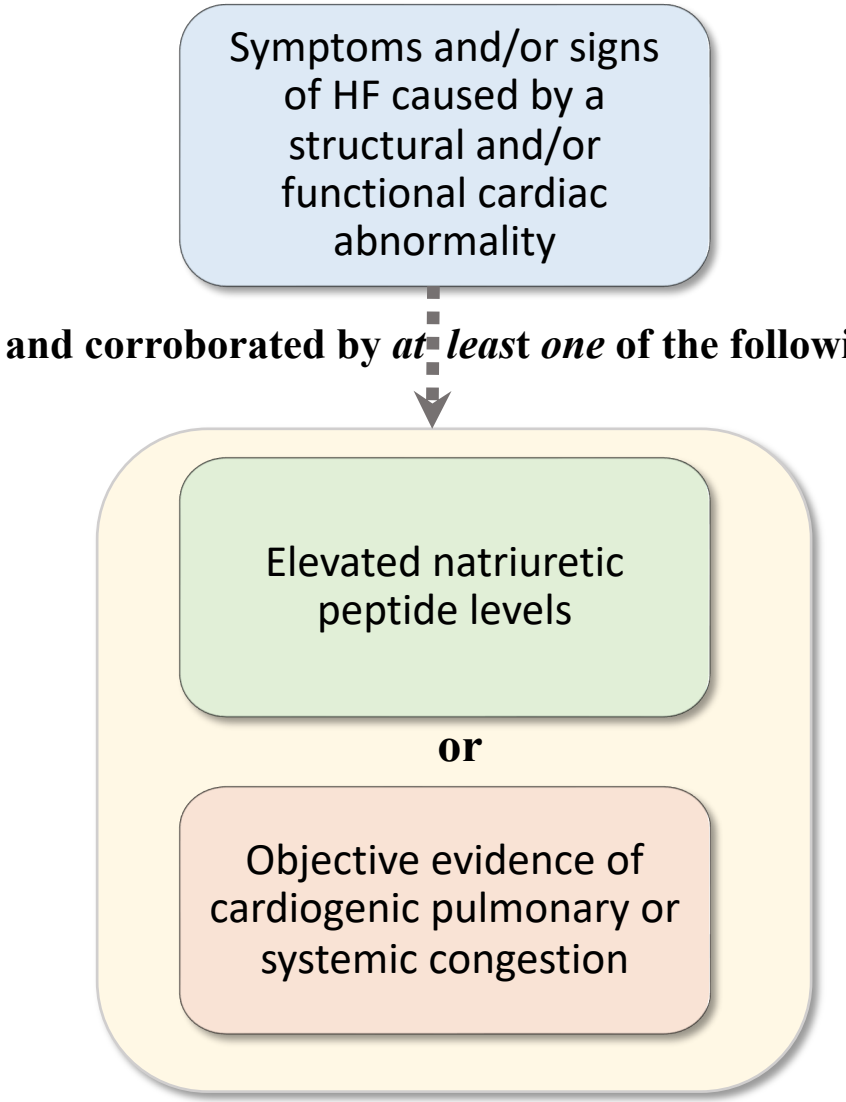
↓ Specificity
↓ Sensitivity in HFpEF, Obesity

Components of a HF Definition

Simple with Adequate Sensitivity and Specificity

1. **Symptoms and Signs**
2. **Cardiac Structural and Functional Abnormality**
3. **Elevated Filling Pressures / Natriuretic Peptides**

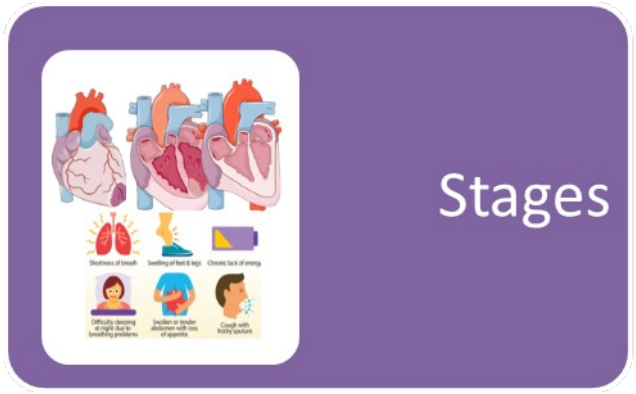
The Universal Definition of HF (UDHF)



HF is a clinical syndrome with current or prior

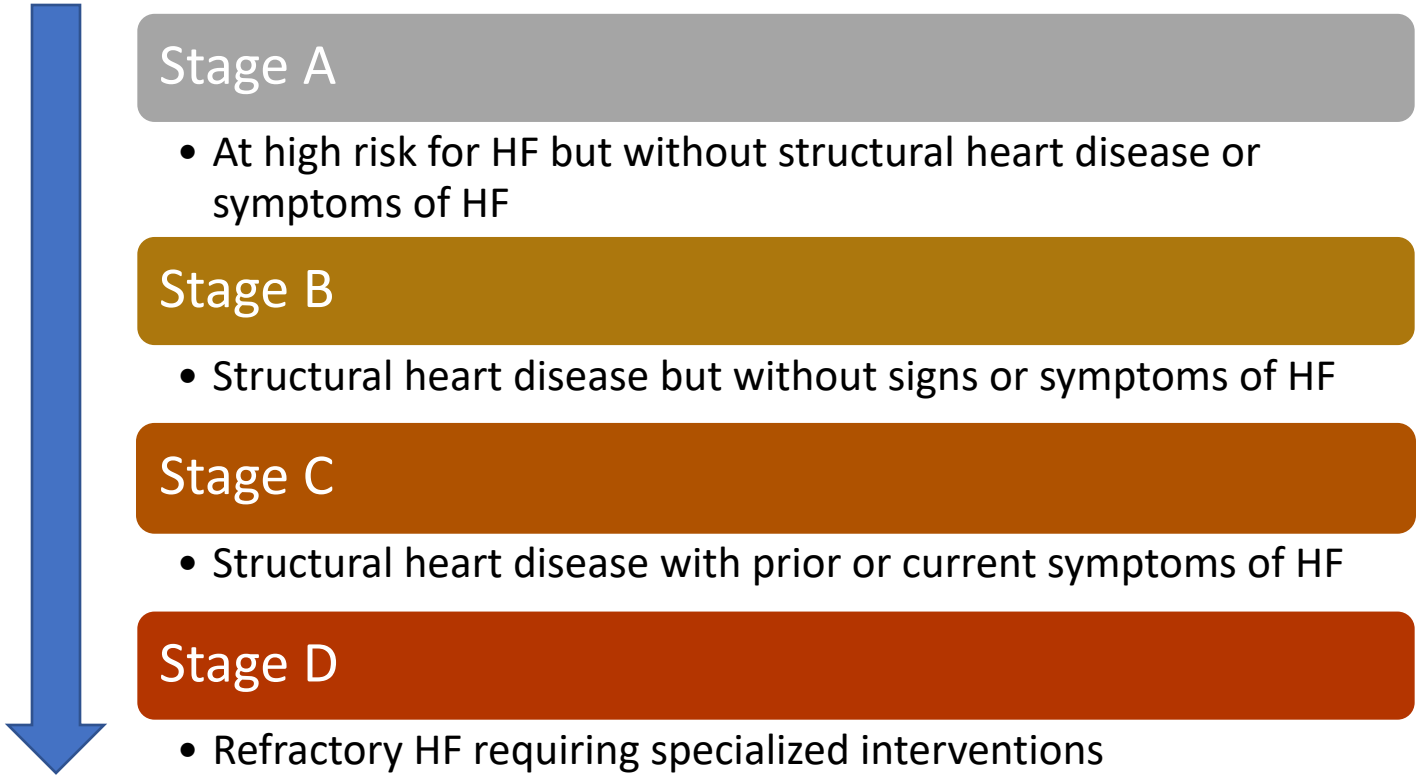
- **Symptoms and or signs caused by a structural and/or functional cardiac abnormality** (as determined by EF<50%, abnormal cardiac chamber enlargement, E/E' >15, moderate/severe ventricular hypertrophy or moderate/severe valvular obstructive or regurgitant lesion)
- **and corroborated by *at least one* of the following:**
  - elevated natriuretic peptide levels
  - objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities such as imaging (e.g. by CXR or elevated filling pressures by echocardiography) or hemodynamic measurement (e.g. right heart catheterization, PA catheter) at rest or with provocation (e.g. exercise)

Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021, ISSN 1071-9164, https://doi.org/10.1016/j.cardfail.2021.01.022.



Revised Stages of HF

ACC/AHA HF Stages



Yancy CW, et al. Circulation. 2013;128(16):e240-327.

HF in the Public Eye

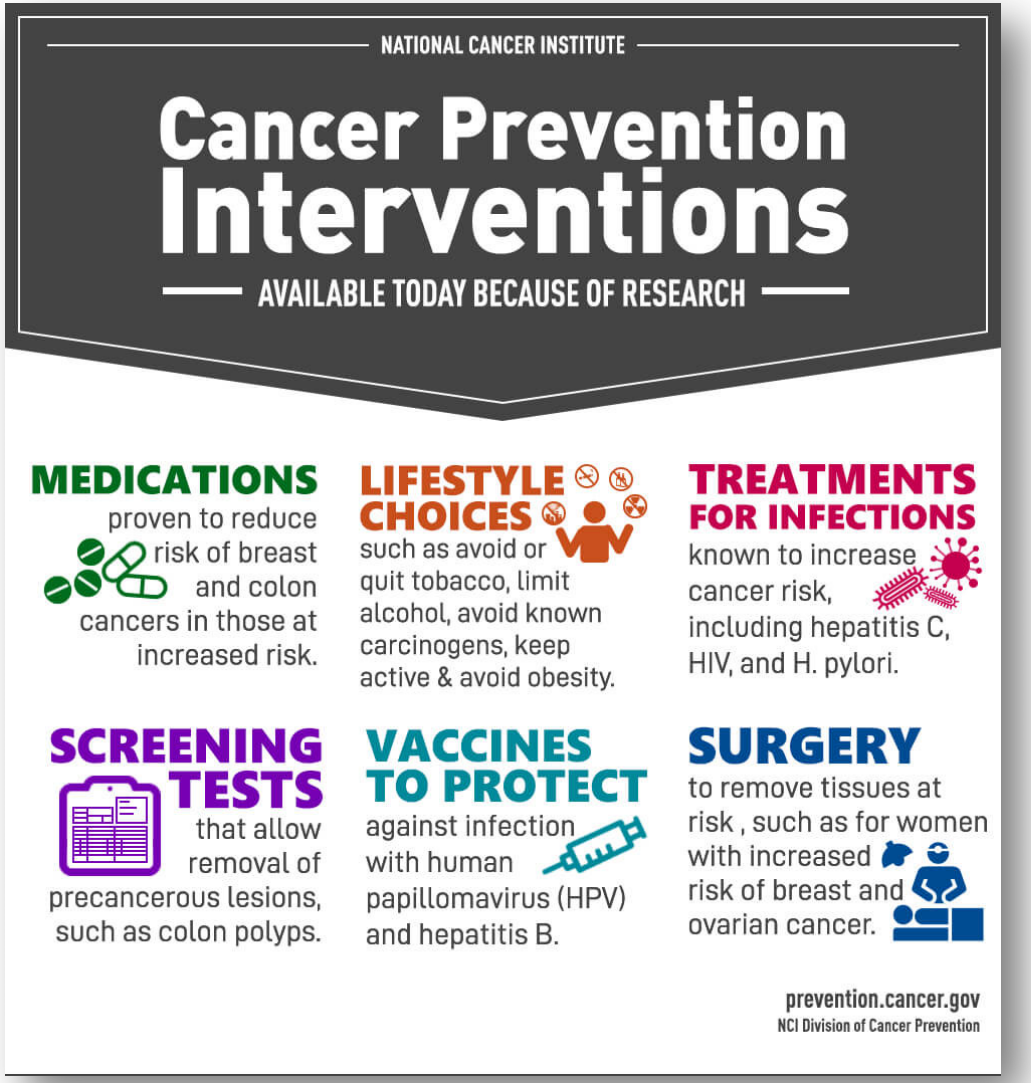
Heart failure

Other names Congestive heart failure (CHF), congestive cardiac failure (CCF)[1][2]

Heart failure

From Wikipedia, the free encyclopedia

Lack of Process for HF Screening and Prevention



Heart Failure Prevention

AWARENESS ? ✖

SCREENING ? ✖

TREATMENT ?

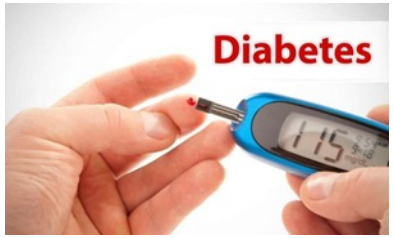
BILLING, CODING, COVERAGE ✖

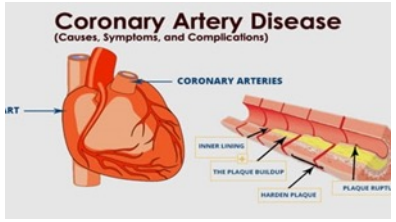
At Risk for HF or Pre-HF (vs Pre-Cancer)

At Risk for HF | Pre-HF | HF | Advanced HF

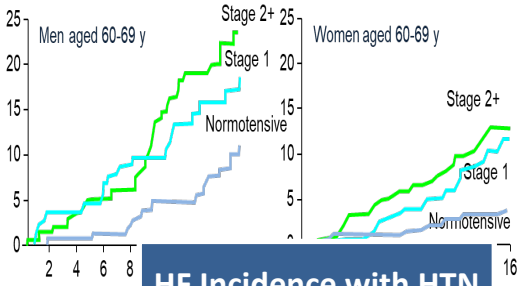
ACC/AHA HF Stage A- Risk

Known

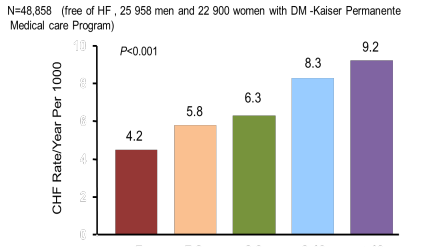




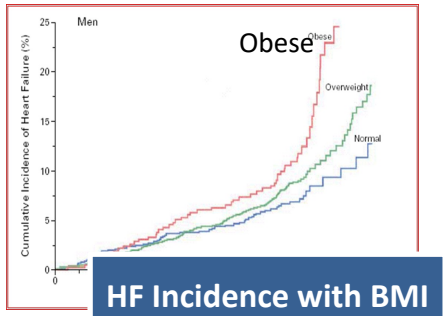
↑Relative Risk



HF Incidence with HTN

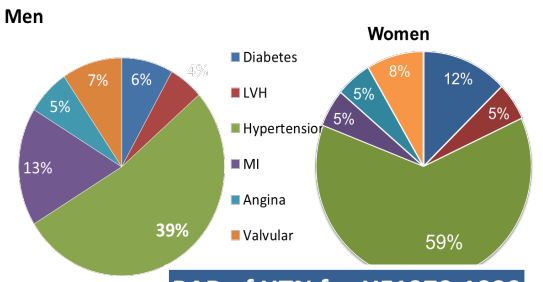


HF Rate with HbA1C

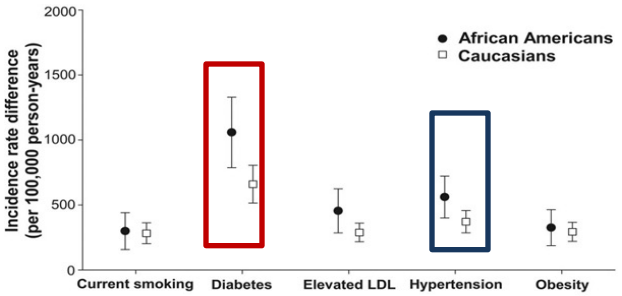


HF Incidence with BMI

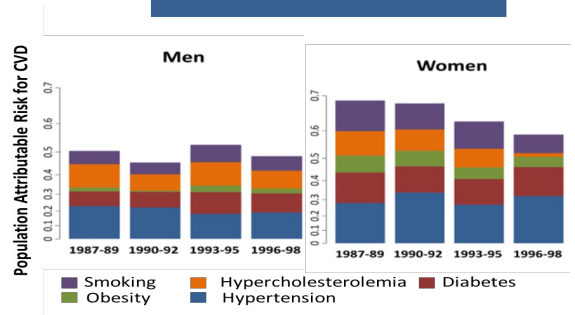
↑Prevalence & Population Attributable Risk (PAR)



PAR of HTN for HF1970-1990



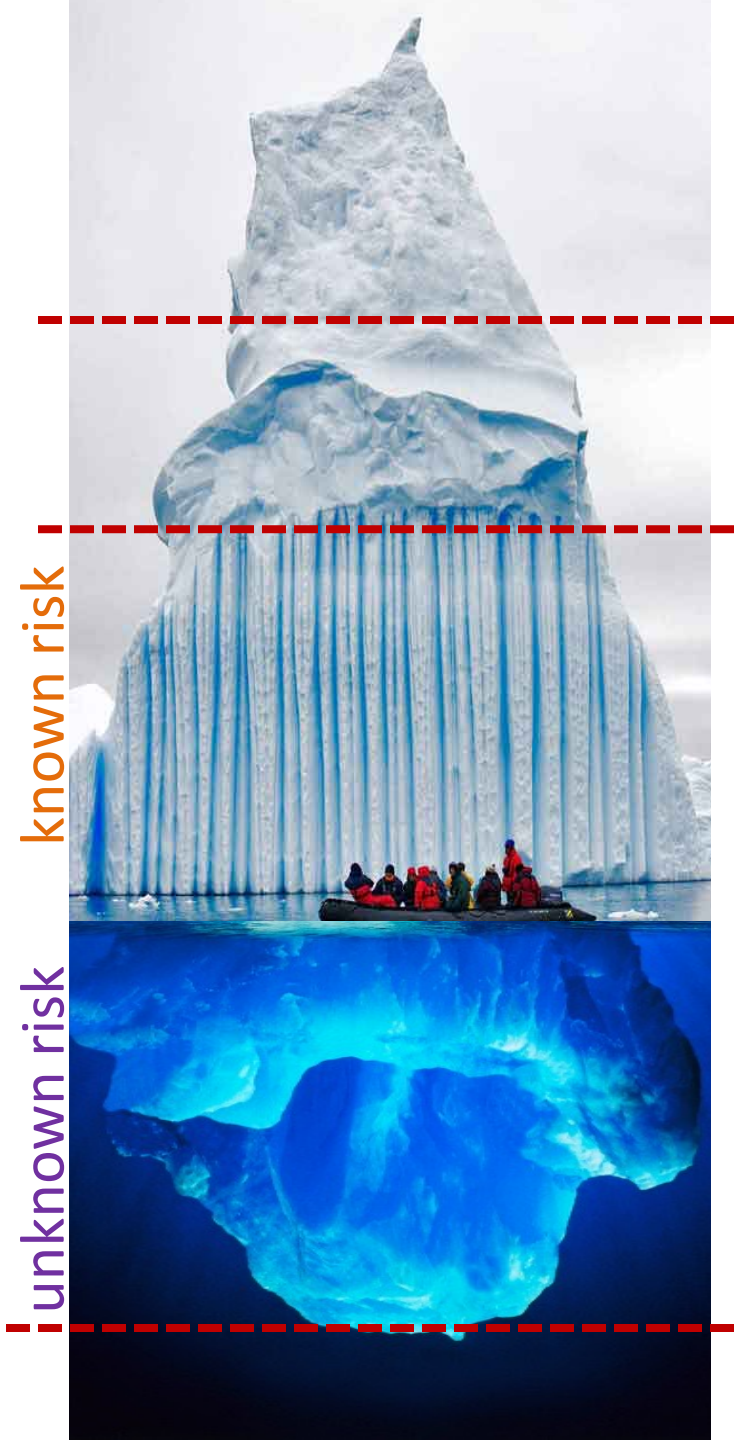
PAR of DM for HF 1987-1998



PAR for CVD

JAMA1996;275:1557-1562. Circulation. 2014 Sep 2; 130(10): 820–828. Circulation 2001;103:2668-2673, N Engl J Med 2002; 347(5):305-313, Circulation. 2014; 130(10): 820–828.

Majority At Risk or Pre-HF



Stage A

Stage B

Stage C/D

26 M DM

92 M Prediabetes

100 M with Obesity

115 M with HTN (AHA)

125 M prevalent any CVD

14 M Post MI

1.1 M HF Hospitalization annually

6.2 M HF Diagnosis

In Olmsted County, 56 % Stage A / B, 12% Stage C, 0.2 % Stage D, 32 % Healthy

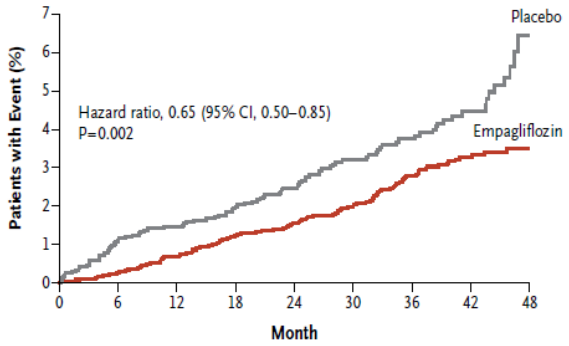
Heart Disease and Stroke Statistics 2020 Update Circulation; ; Heidenreich PA et al. *Circulation*. 2011 Mar 1;123(8):933-44, Ammar et al. Circulation. 2007 Mar 27;115(12):1563-70.

SGLT2i Prevents HF in Patients with CV Risk

EMPA-REG OUTCOME TRIAL

~ 10% pre- existing HF, 43% on loop diuretics baseline

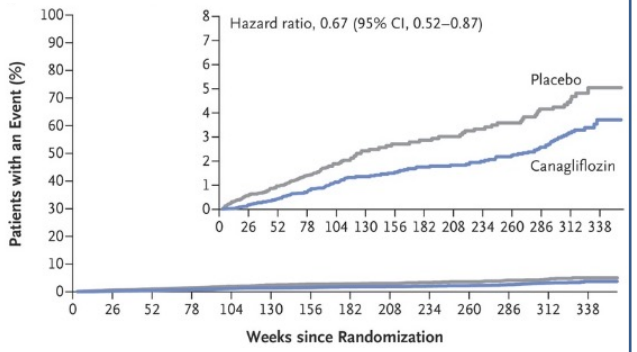
Hospitalization for HF



CANVAS TRIAL

14% had pre- existing HF

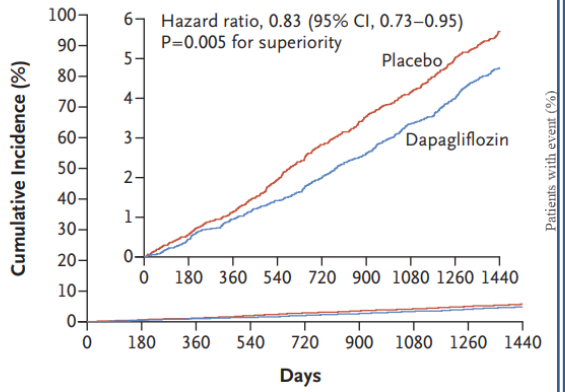
Hospitalization for HF



DECLARE TRIAL

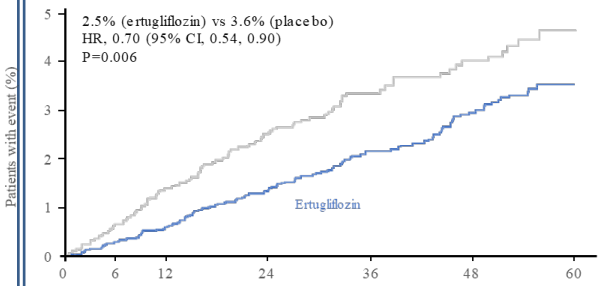
CVD AND HFH

Cardiovascular Death or Hospitalization for Heart Failure



VERTIS CV TRIAL

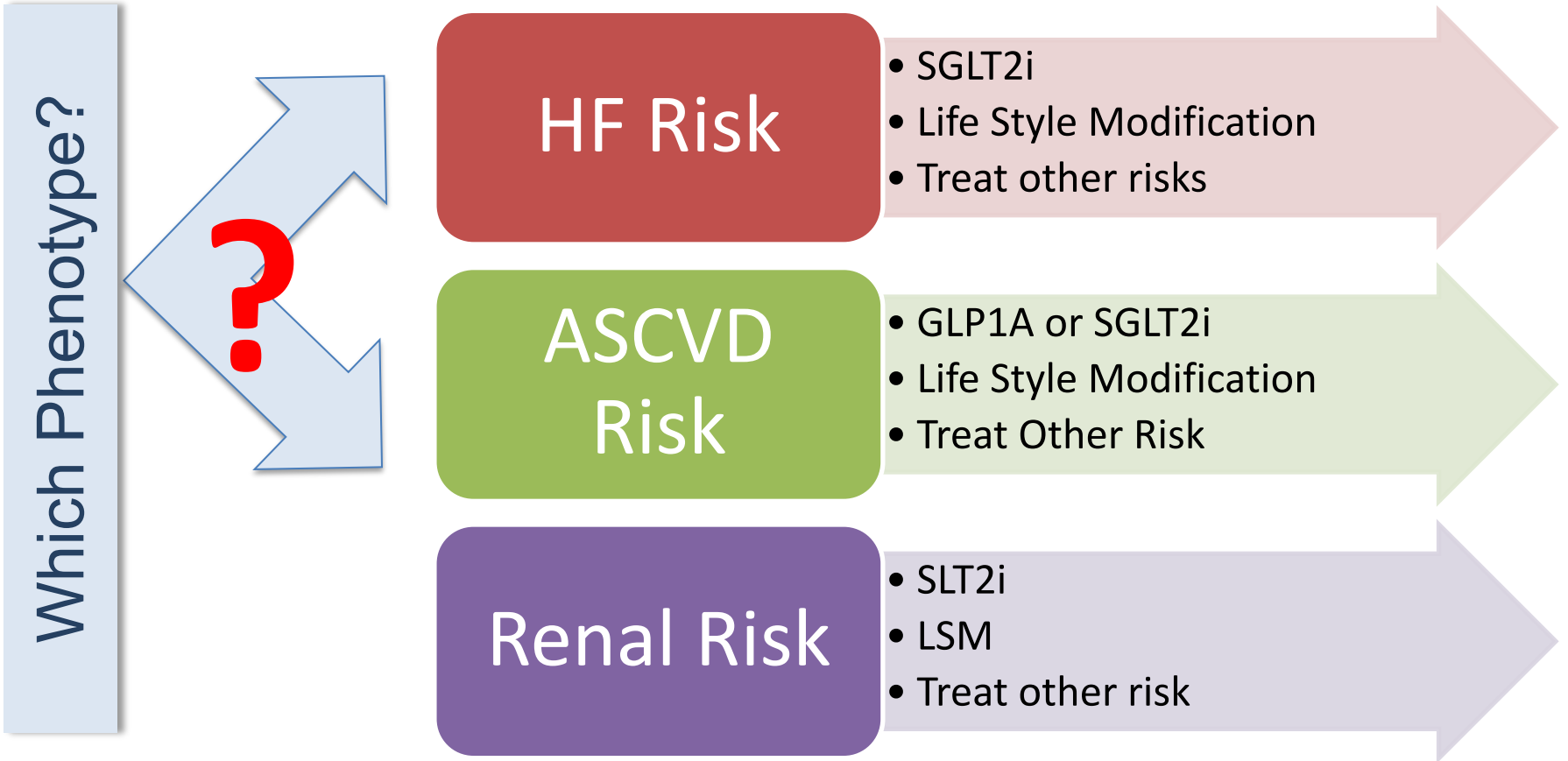
Hospitalization for HF



- **HF Events Reduced/ Prevented with SGLT2i in high risk CVD**
- Weight reduced by ~2 kg with SGLT2i
- 30-35 % RRR in HFH

N Engl J Med 2015;373:2117-28. N Engl J Med. 2017; 377:644–657 N Engl J Med 2019; 380:347-357
Cannon CP, et al. Results of the VERTIS CV Trial. Presented at: 80th ADA Scientific Sessions; June 16, 2020. Symposium.

Patient with DM without Symptomatic HF



Role of Biomarkers

STOP- HF Trial RCT (n=1374)

BNP testing baseline & annually

STOP HF

INTERVENTION (KNOW BNP)

BNP ≥ 50 ng/L

CV referral, cardiologist led W/U & team management

Doppler Echocardiography

Risk factor management, coaching by specialist nurse on adherence, LSM

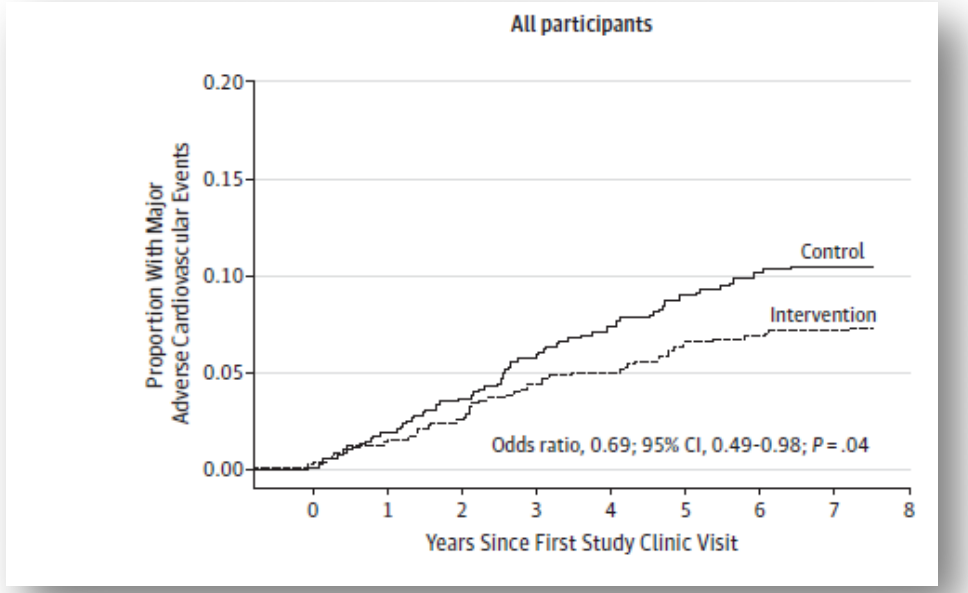
Collaborative care, annual specialized CV review

Repeat echocardiography, BNP, other

BNP < 50 ng/L

Same as control

CONTROL (NO KNOWLEDGE OF BNP)

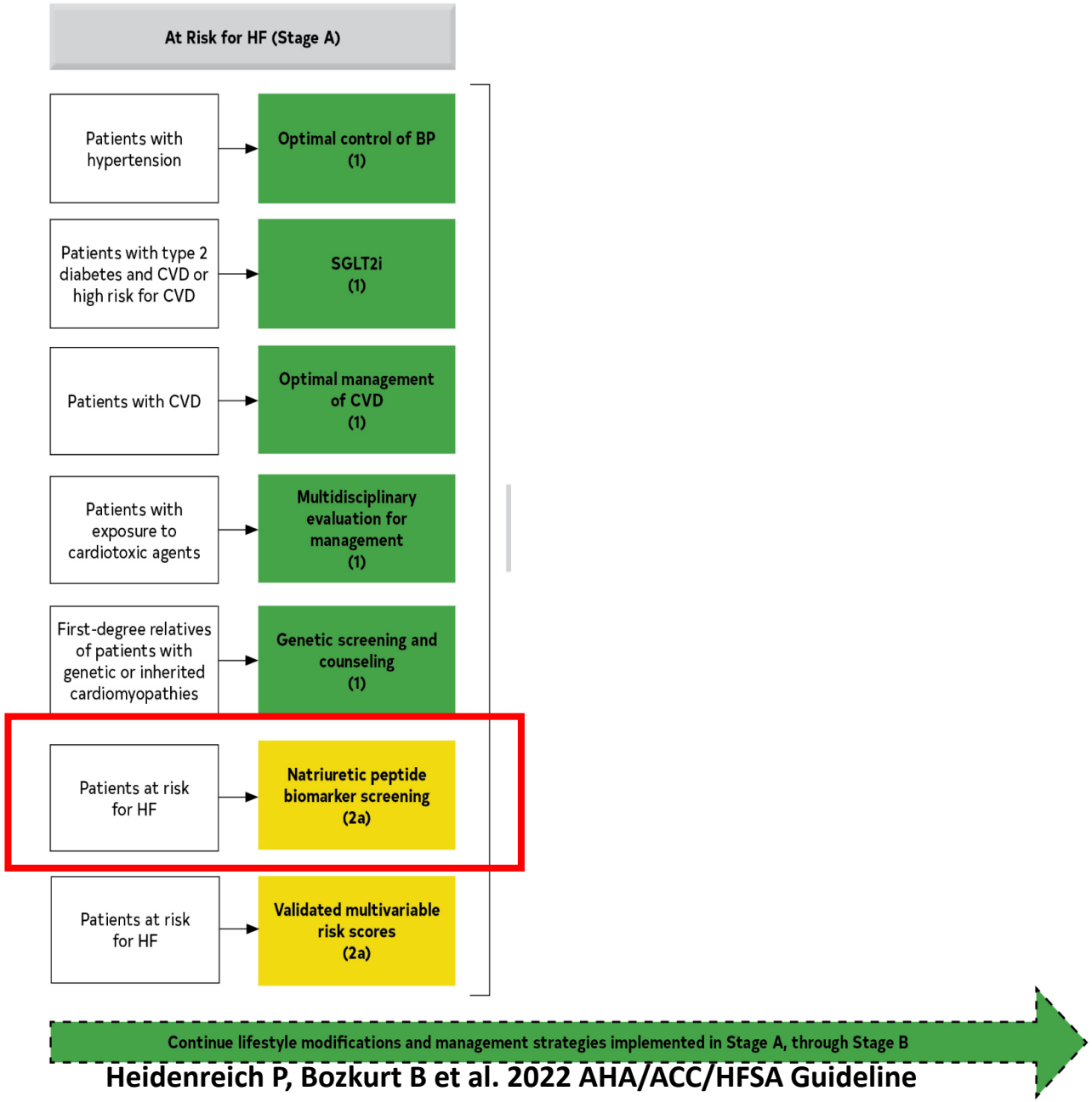


Ledwidge et al.JAMA. 2013 Jul 3;310(1):66-74.

Patients at Risk for HF (Stage A: Primary Prevention) (con't.)

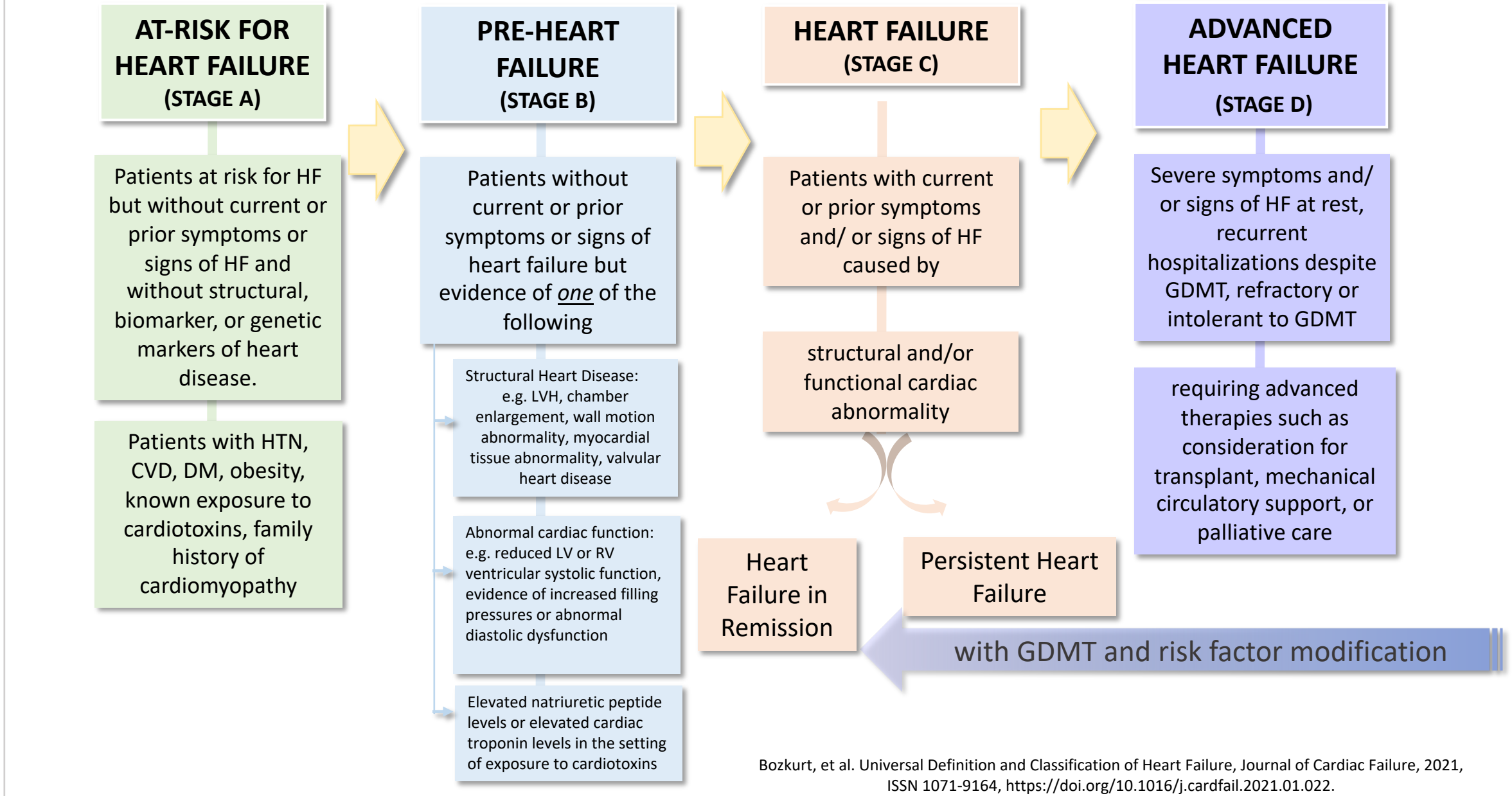
2a	B-R	4. For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF.

Recommendations for Patients at Risk of HF (Stage A) and Those With Pre-HF (Stage B)



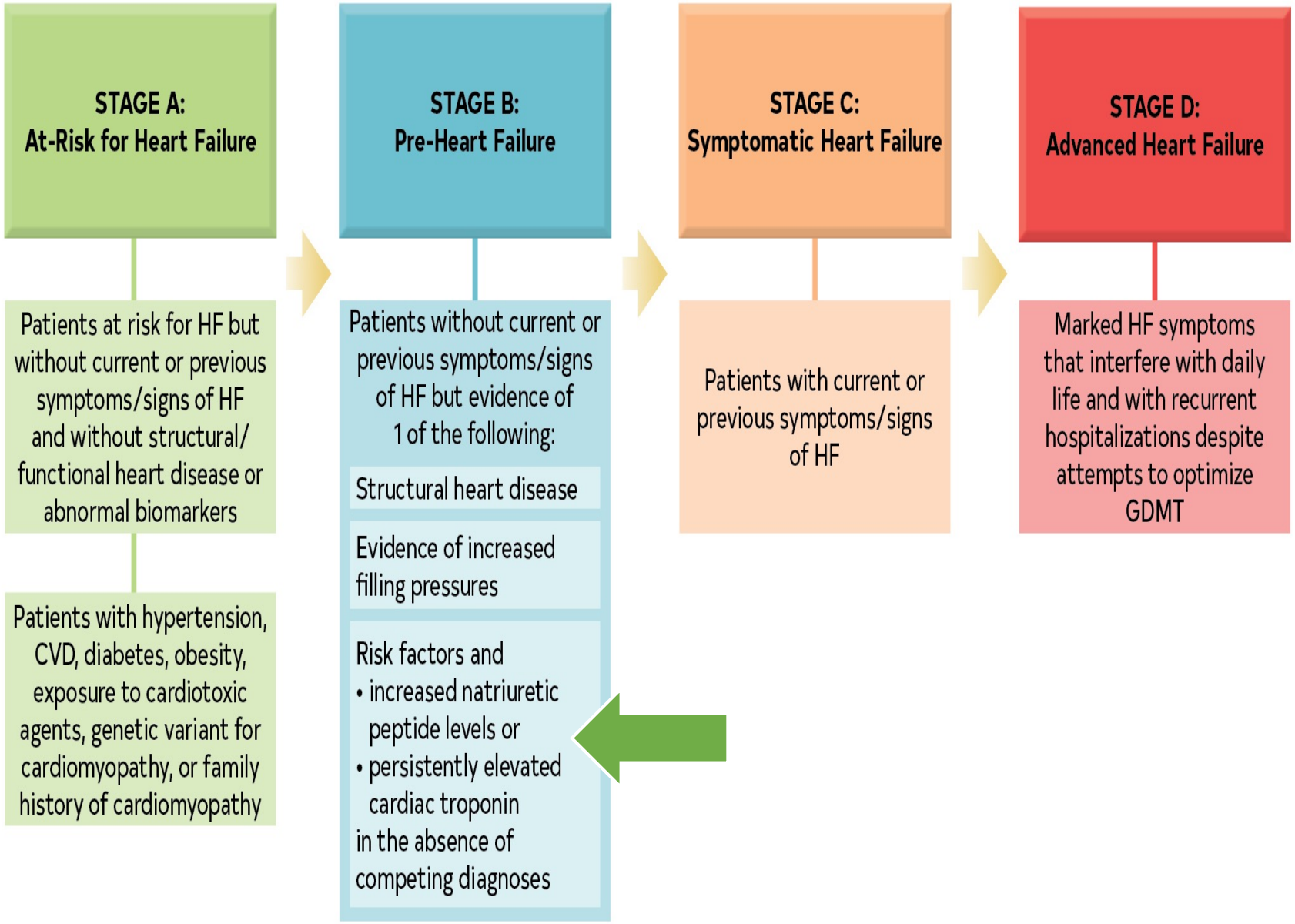
Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline

Universal Definition Stages of HF



Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021, ISSN 1071-9164, https://doi.org/10.1016/j.cardfail.2021.01.022.

ACC/AHA Stages of HF



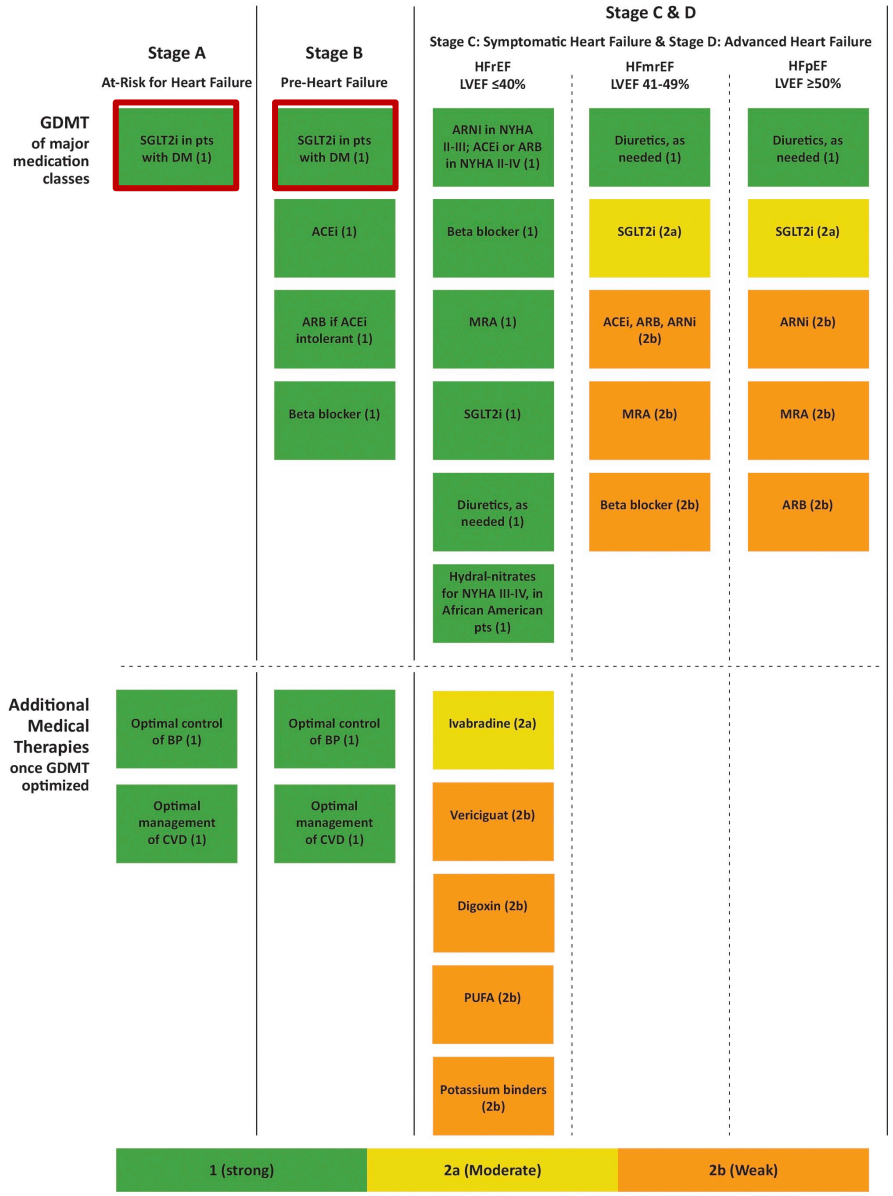
AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

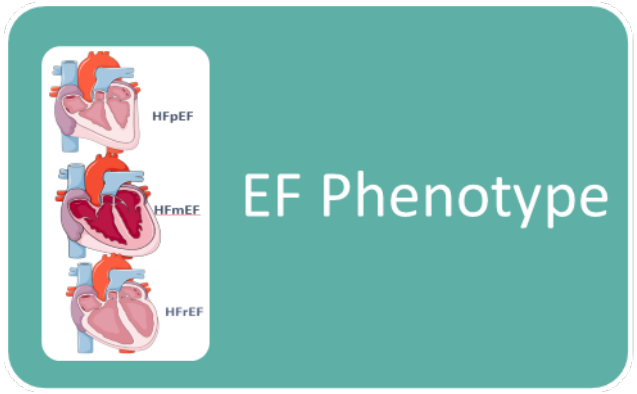
CENTRAL ILLUSTRATION: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Guideline Directed Medical Therapy Across Heart Failure Stages

Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.



Heidenreich PA, et al. J Am Coll Cardiol. 10.1016/j.jacc.2021.12.012



EF CLASSIFICATION

EF Classification of HF in Universal Definition

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 ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%

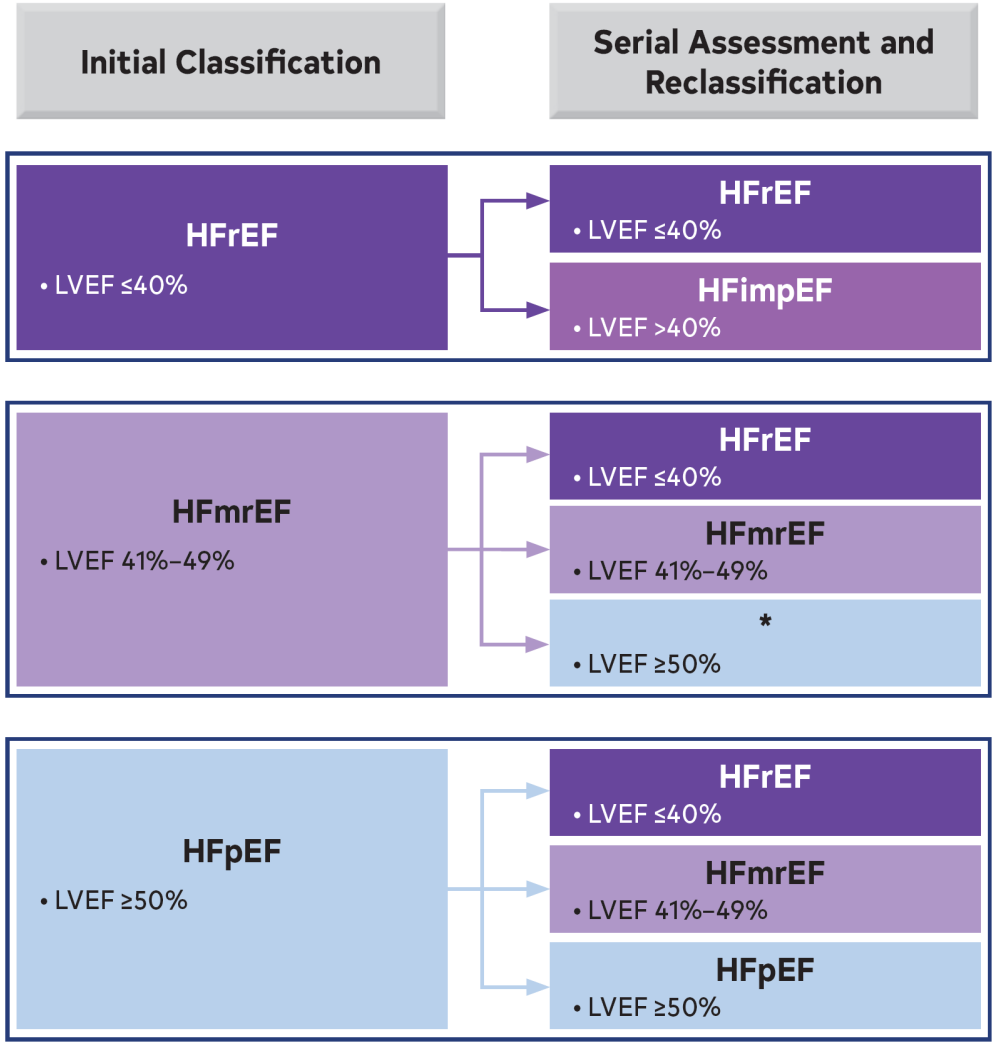
Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021, ISSN 1071-9164.

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

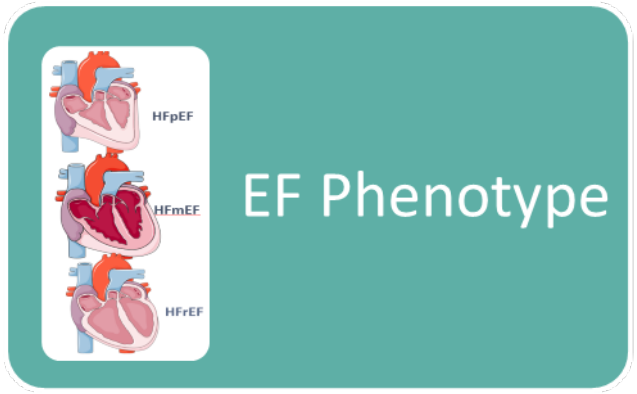
Endorsed by the Heart Failure Society of America

Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline
https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

Classification and Trajectories of HF Based on LVEF



Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

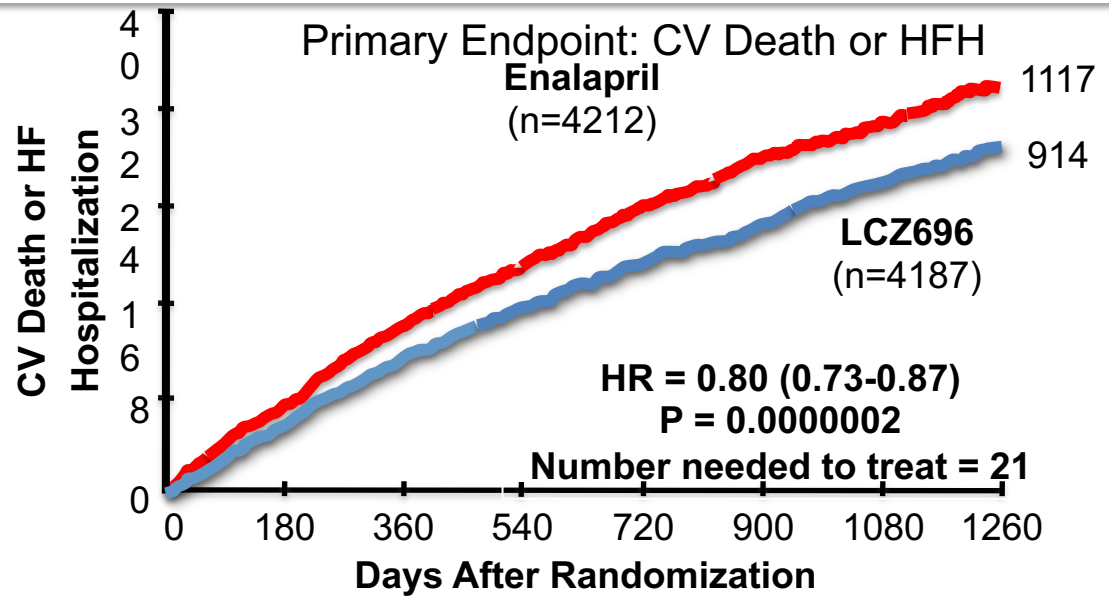


TREATMENT ACCORDING TO EF CLASSIFICATION IN GUIDELINES

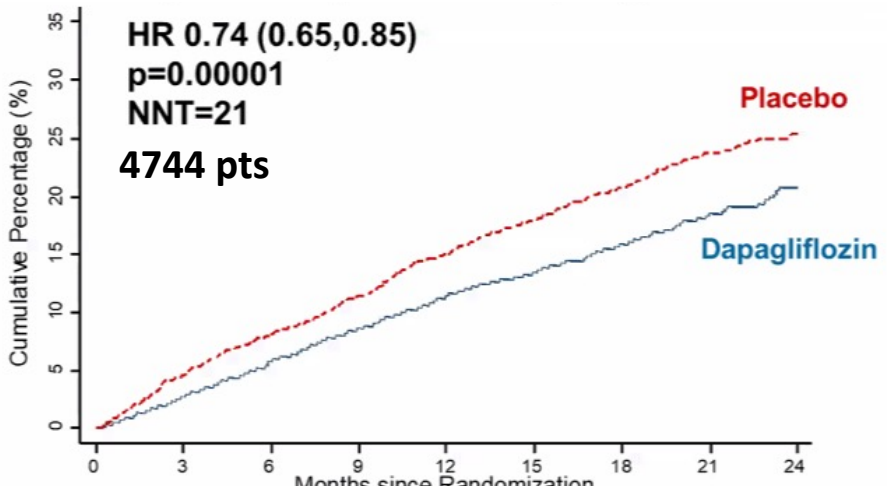
Current Evidence in Treatment of HFrEF

ARNi & SGLT2i in HFrEF

PARADIGM



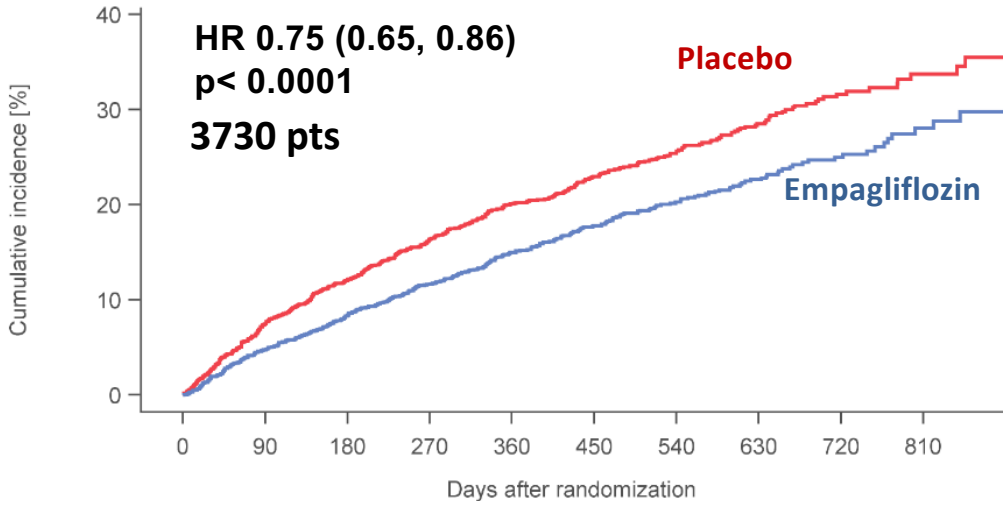
DAPA-HF



55% was without DM, 41 % had CKD

N Engl J Med 2019;381:1995-2008

EMPEROR-Reduced



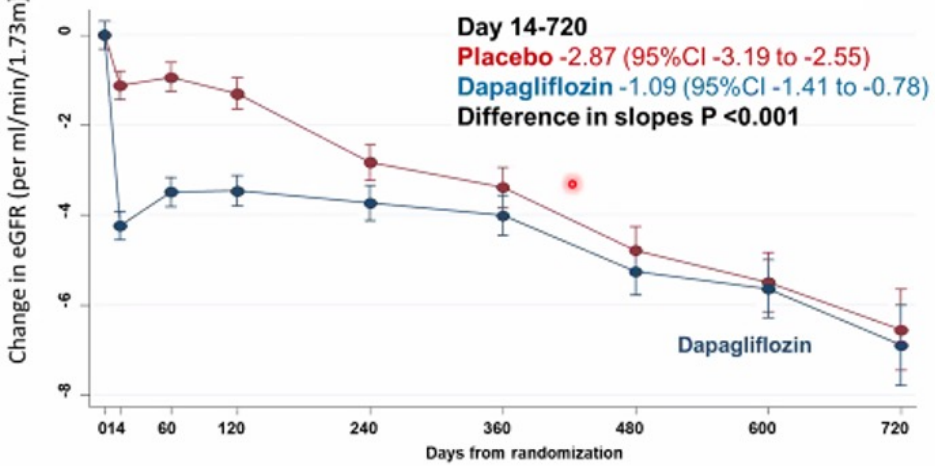
50% was without DM, 48 % had CKD

Packer M et al. NEJM, August 29

Renal Benefits in HFrEF

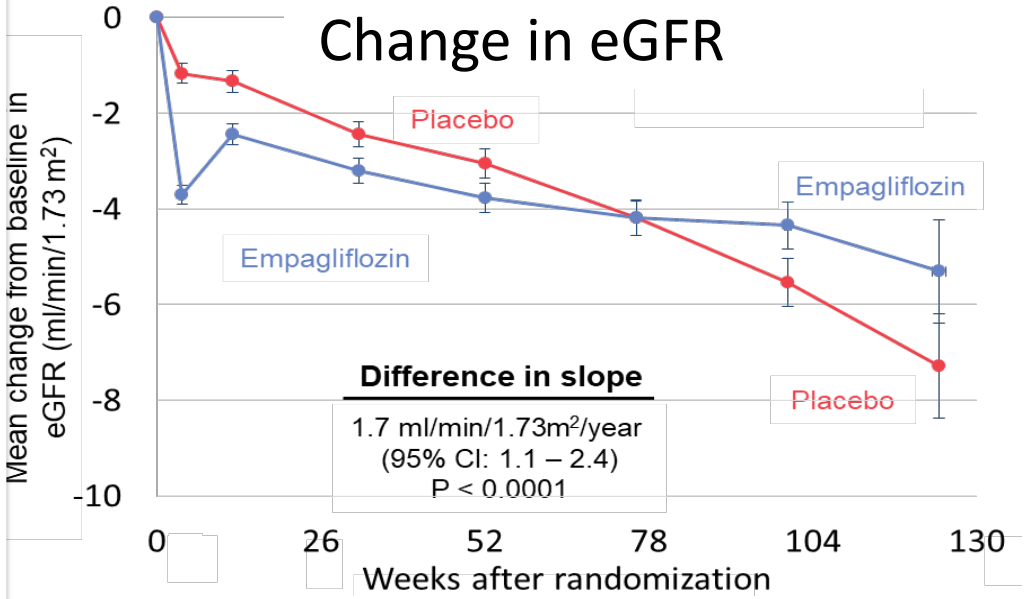
DAPA-HF

Change in eGFR



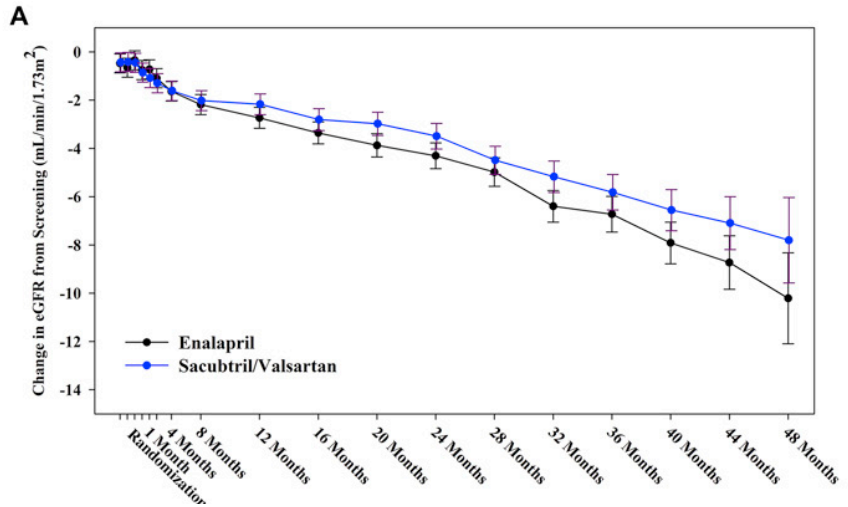
EMPEROR-Reduced

Change in eGFR

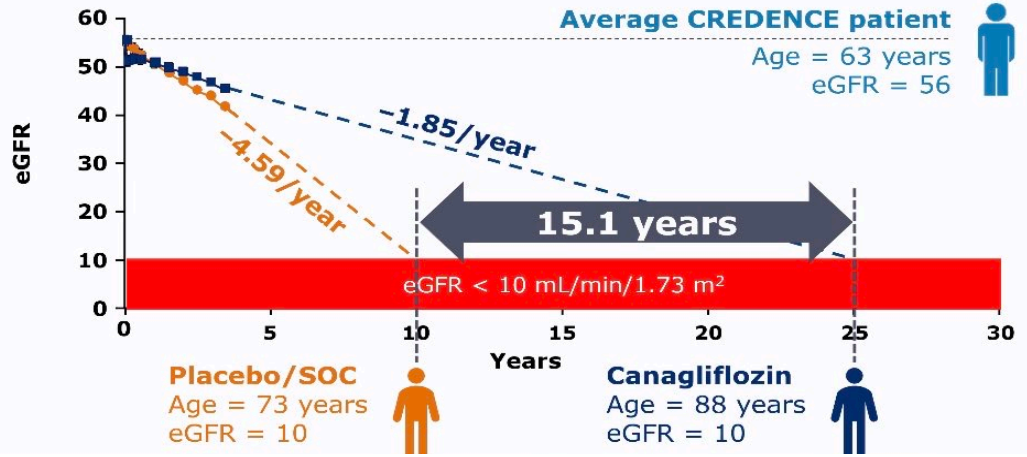


PARADIGM

Difference=1.78 ml/min/yr



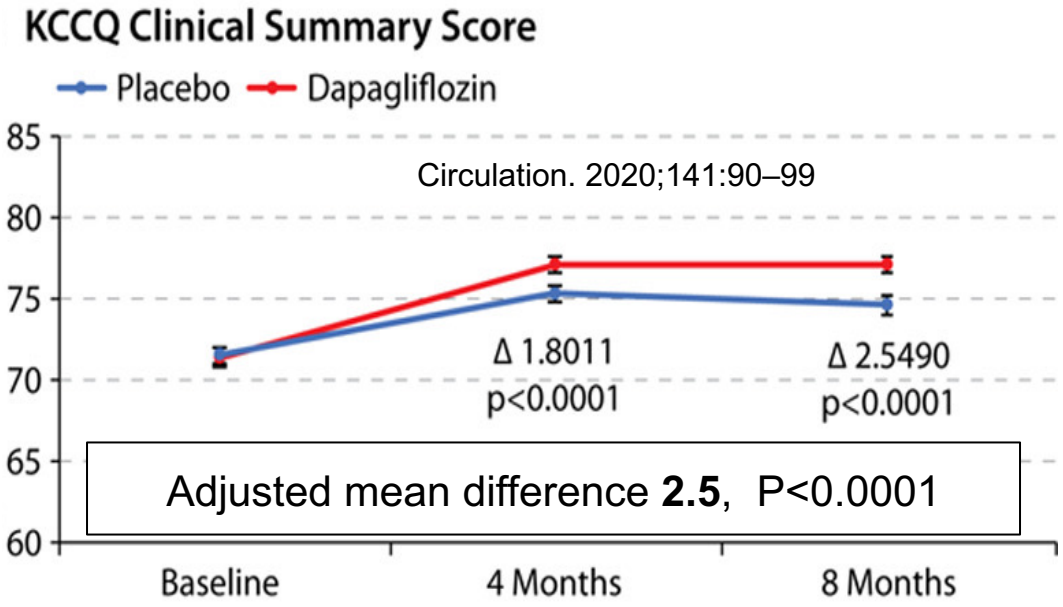
Difference=1.73 ml/min/yr



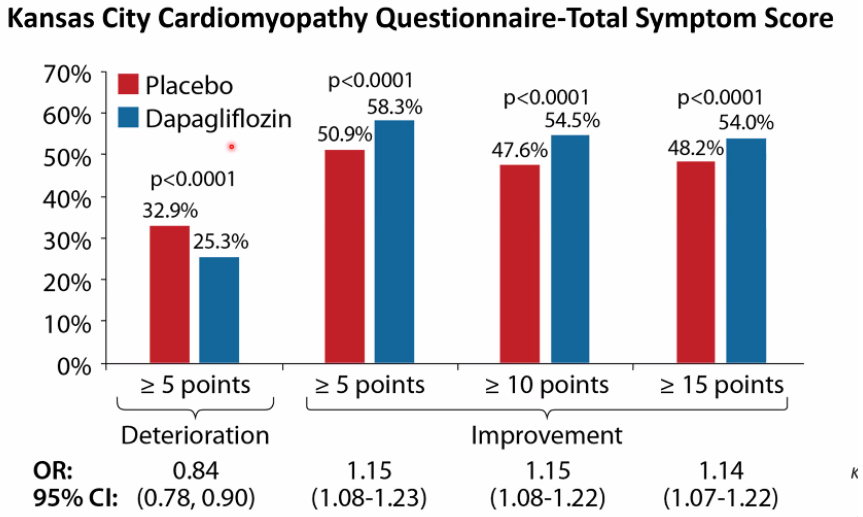
N Engl J Med 2019;381:1995-2008, NEJM, August 29 2020, JACC Heart Fail. 2018 Apr, 6 (6) 489–498

QoL Benefit in HFrEF

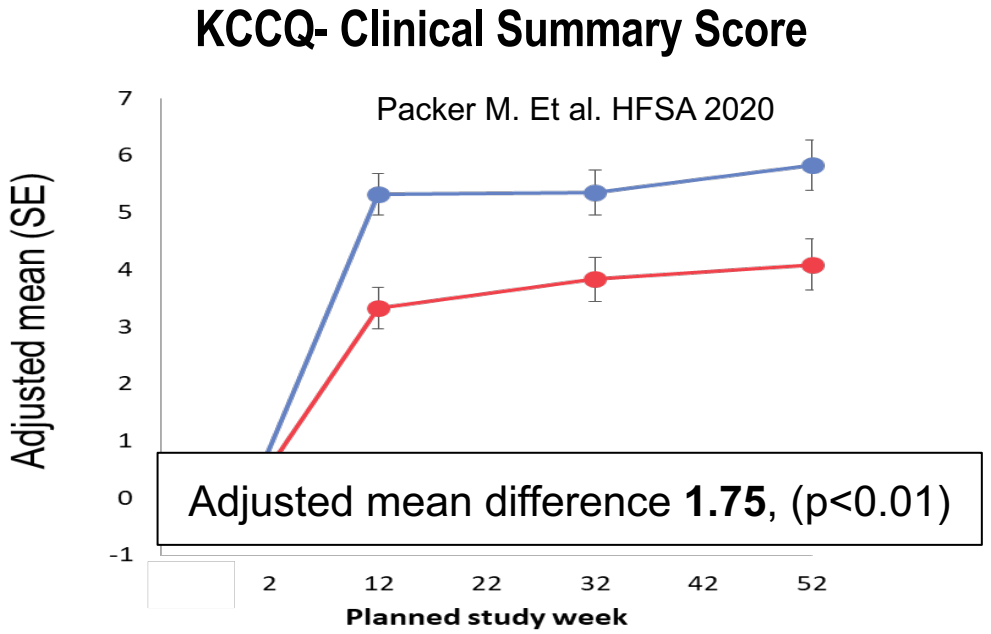
DAPA-HF



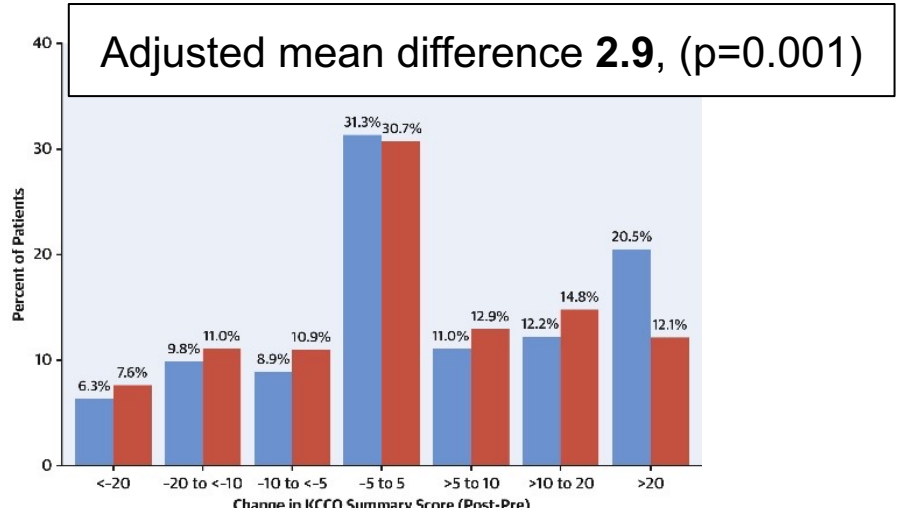
DAPA-HF



EMPEROR-Reduced



PARADIGM



Khariton Y. et al. J Am Coll Cardiol HF. 2019; 7(11):933-41

Outcomes – with Patient's Perspective

Symptoms | QOL

Reverse Remodeling

Prevent HF Hospitalizations

Improve Survival

Medications	QOL	Reverse Remodeling	Prevent Hospitalizations	Improve Survival
Diuretics	~~	X		X
ACEi / ARB	~ ~	Halts remodeling	✓	✓
ARNi	✓	✓	✓	✓
BB	X	✓✓	✓	✓
MRA	X	✓	✓	✓
SGLT2i	✓	✓	✓	✓
Hyd+ISDN in AA	✓	(load dependent)	✓	✓
Ivabradine	✓	✓	✓	X
Digoxin	✓		✓	X
Vericiguat	?	X	✓	X

Safety Against Comparator

ARNi against ACEi (Paradigm)

- Higher risk of symptomatic hypotension
- Lesser risk of WRF
- Lesser risk of hyperkalemia
- Comparable angioedema
- Fewer SAE resulting in discontinuation

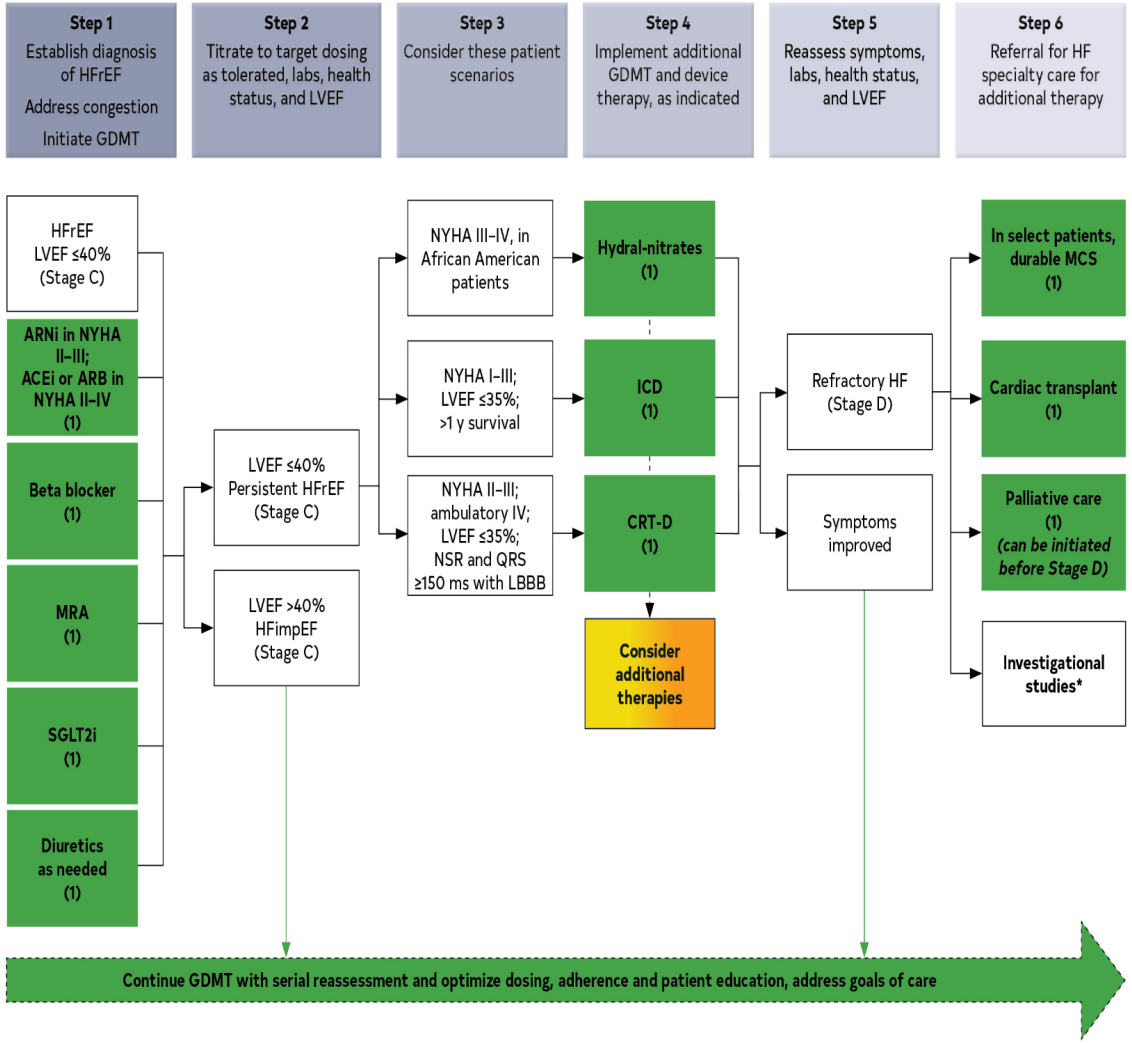
SGLT2i against placebo

- **Higher risk of genital tract infection**
- Fewer SAE
- No excess risk of volume depletion
- No excess risk of symptomatic hypotension
- **No excess risk of hypoglycemia** regardless of diabetes status
- No excess risk of ketoacidosis
- **No excess risk of hyper or hypokalemia or WRF**
- Regardless of diabetes, age, renal function, BP or concurrent ARNi therapy

Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF.

Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication.

Medication doses should be increased to target as tolerated.



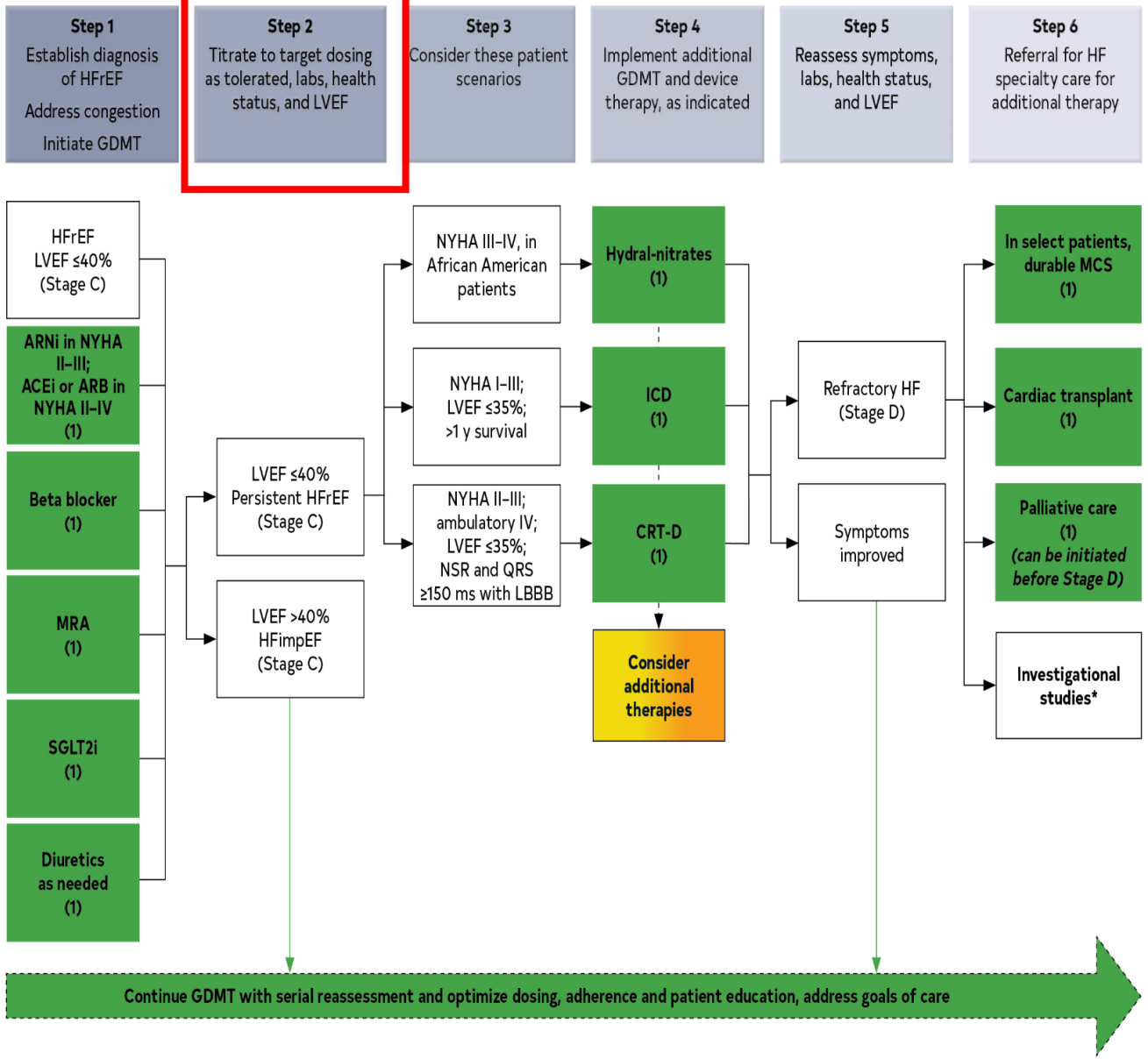
Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

Step 2

Titrate to target doses once all 4 classes of medications initiated

Treatment of HFrEF Stages C and D

STEP 2

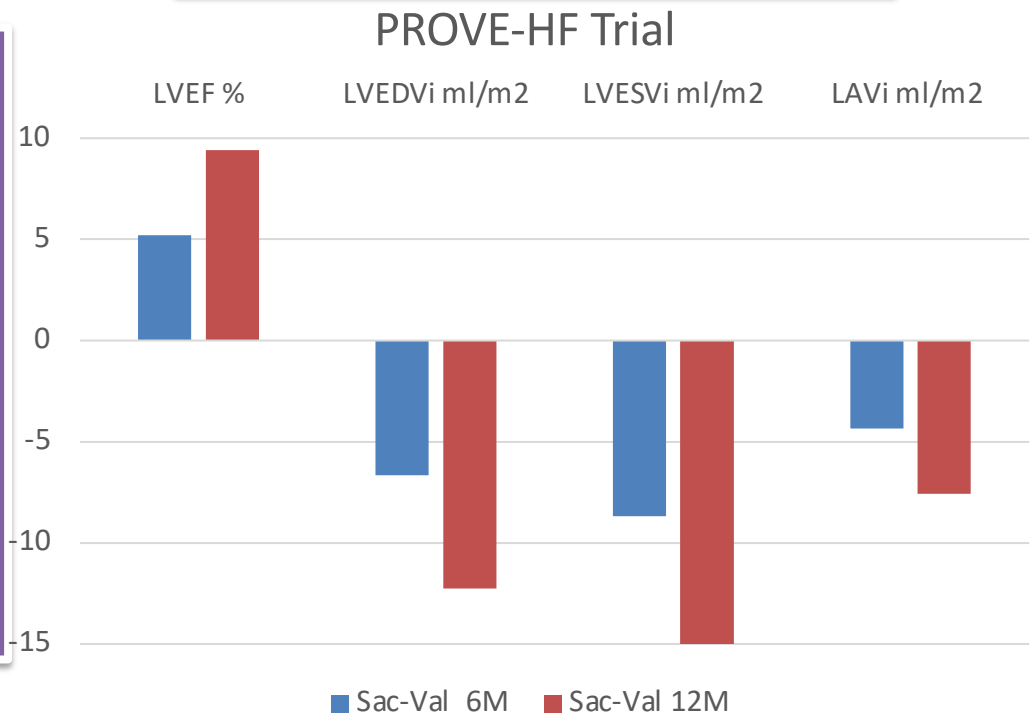


Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

Reversal of Remodeling with GDMT

ARNi

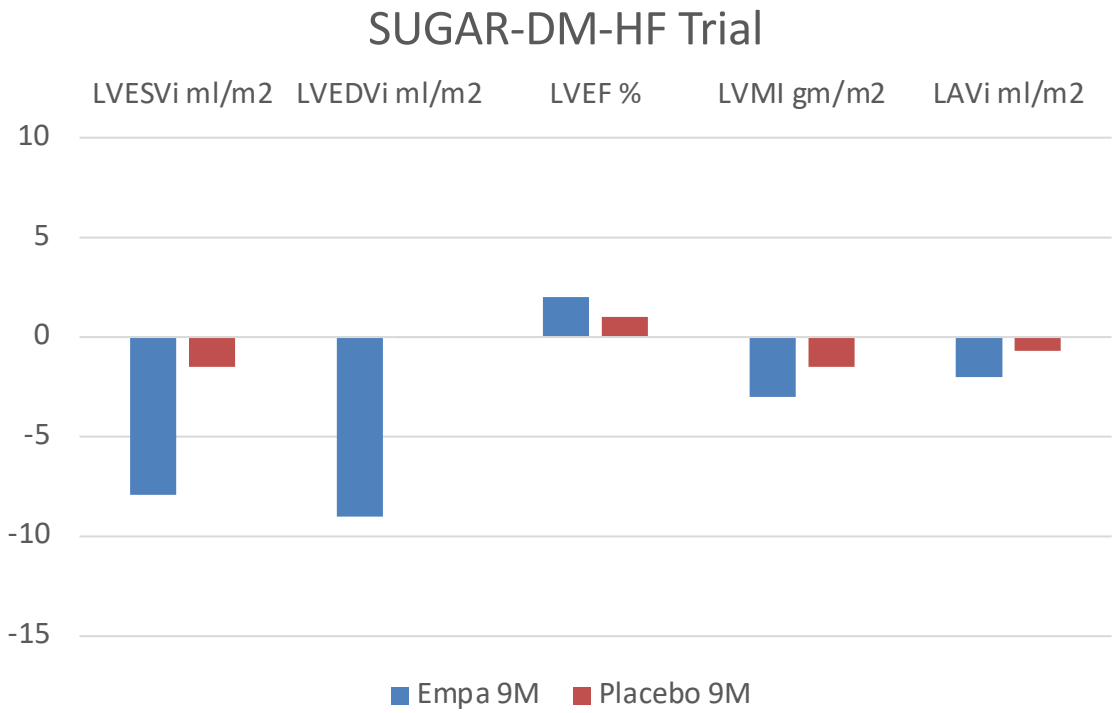
12 months in PROVE HF



JAMA. 2019;322(11):1085-1095.

SGLT2i

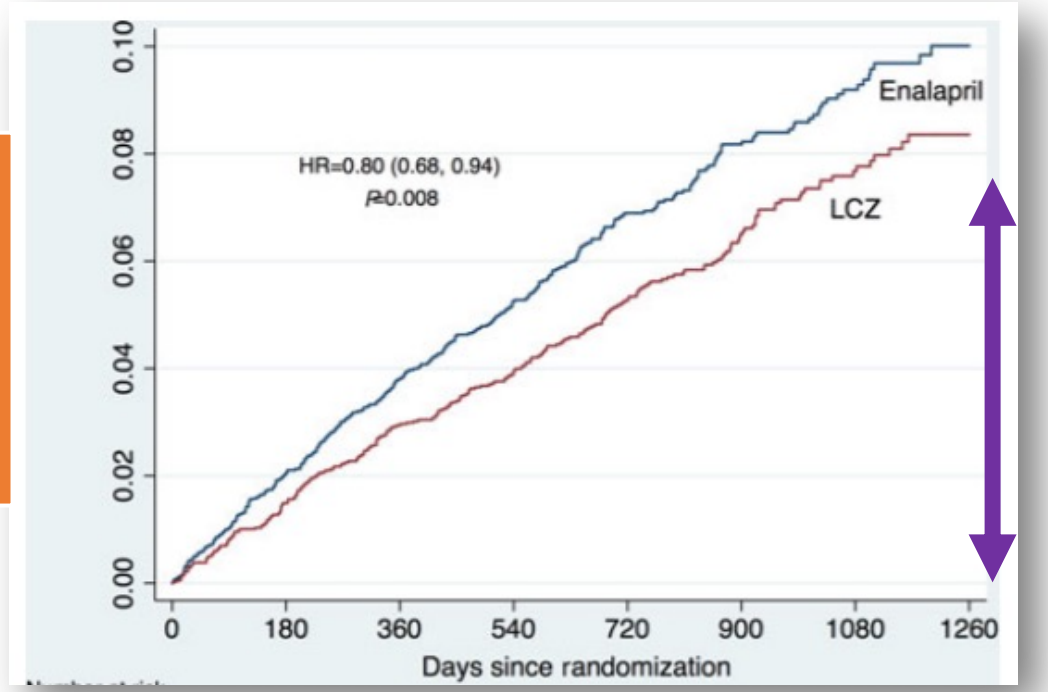
9 months in SUGAR DM



Lee M. Et al. Circulation. 2021;143:516–525.

Reduced SCD with GDMT

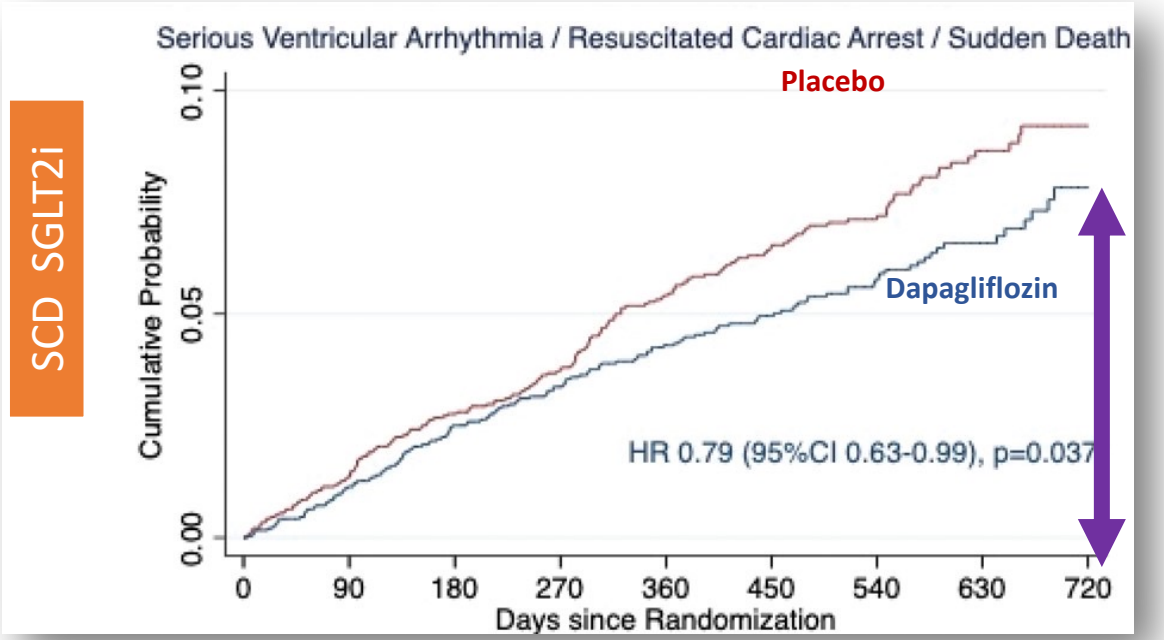
SCD ARNi



Desai AS. Et al Eur Heart J. 2015 Aug 7;36(30):1990-7. PMID: 26022006

SCD Placebo 3.3/1000 pt-yr, Dapagliflozin 2.7/1000 pt-yr, HR: 0.81 (0.62-1.07)

SCD SGLT2i



Curtain J. et al. DAPA-HF Eur Heart J . 2021 Sep 21;42(36):3727-3738.

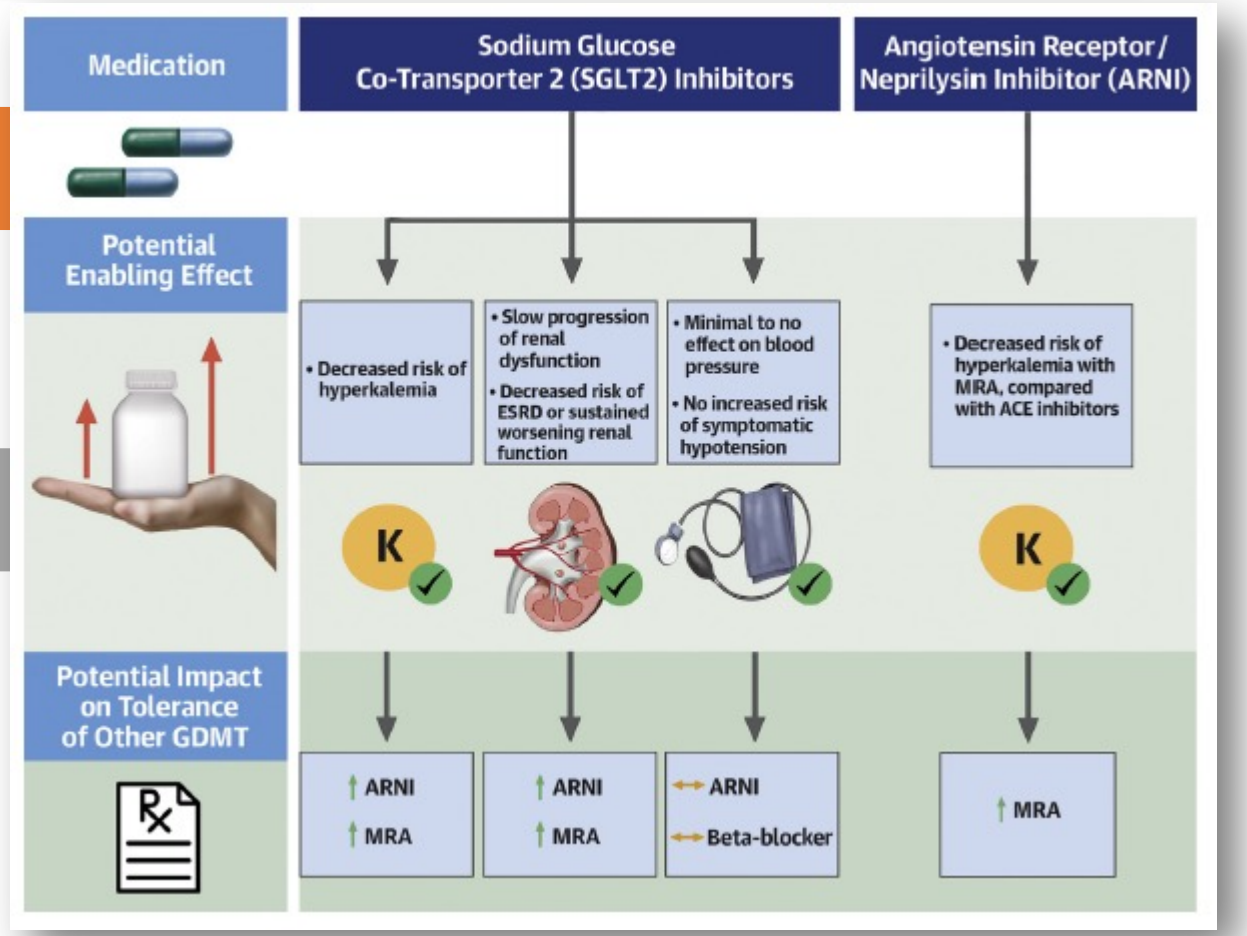
New Agents Enable Initiation of Other GDMT

SGLT2i

- Reduction in decline in eGFR
- No increase in hyperkalemia
- Less MRA discontinuation

ARNi

- Lower K levels or hyperkalemia
- Reduction in decline in eGFR



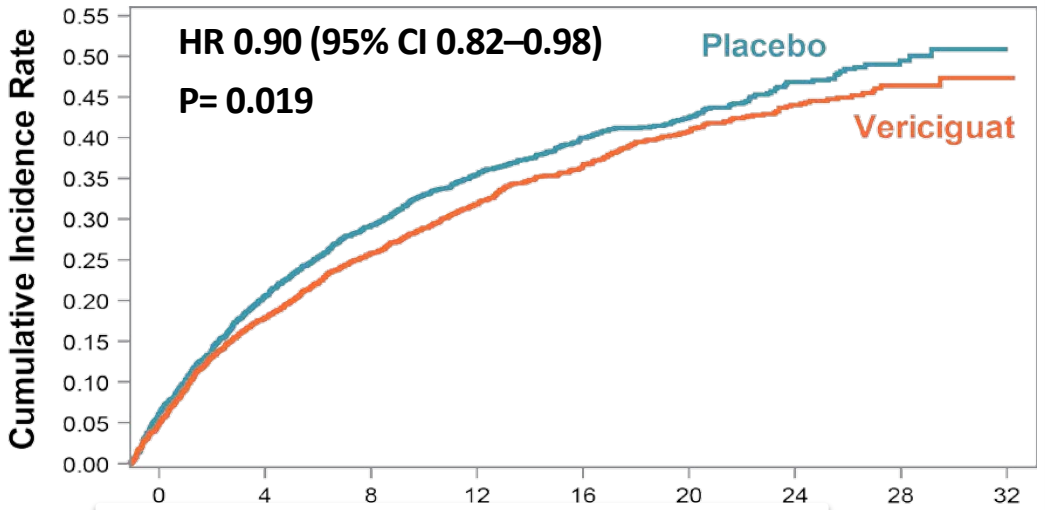
Desai A JAMA Cardiology 2016, Ferreira et al. JACC 77:11, 23 March 2021, 1397-1407, Greene JACC 77 2021

Recent Evidence for Additional Therapies in HFrEF

Vericiguat and Omecamtiv (not FDA approved)

Primary Endpoint: CV Death or HFH

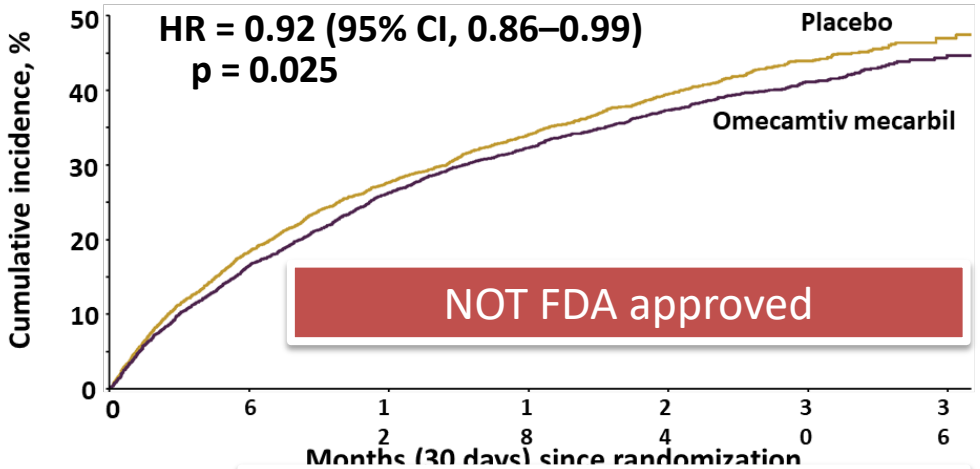
VICTORIA



Inclusion:
- NYHA class II-IV, recent HFH/IV Diur
- LVEF < 45%
- NT-proBNP ≥1000 pg/ml*

Exclusion:
- eGFR <15 ml/min/1.73 m^2
- SBP <100mmHg

GALACTIC-HF



Inclusion:
- NYHA class II-IV, current HF Hosp or HF Hosp/UC within 1 yr
- LVEF ≤ 35%
- NT-proBNP ≥400 pg/ml*

Exclusion:
- eGFR <20 ml/min/1.73 m^2
- SBP <85 mmHg

No reduction in CV Death

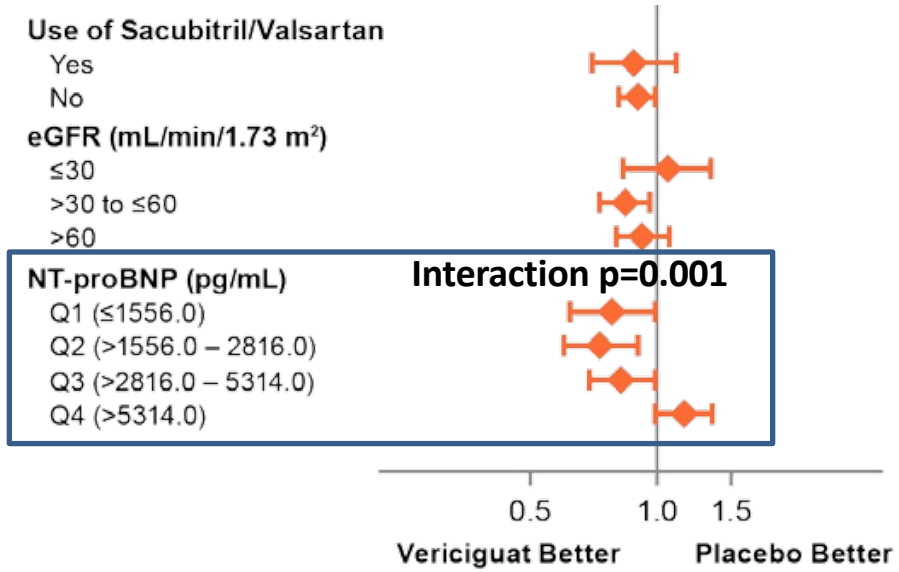
Armstrong P et al. N Engl J Med 2020;382:1883-93.

Teerlink J et al. N Engl J Med 2020; 11/13/2020, *AHA LBCT*

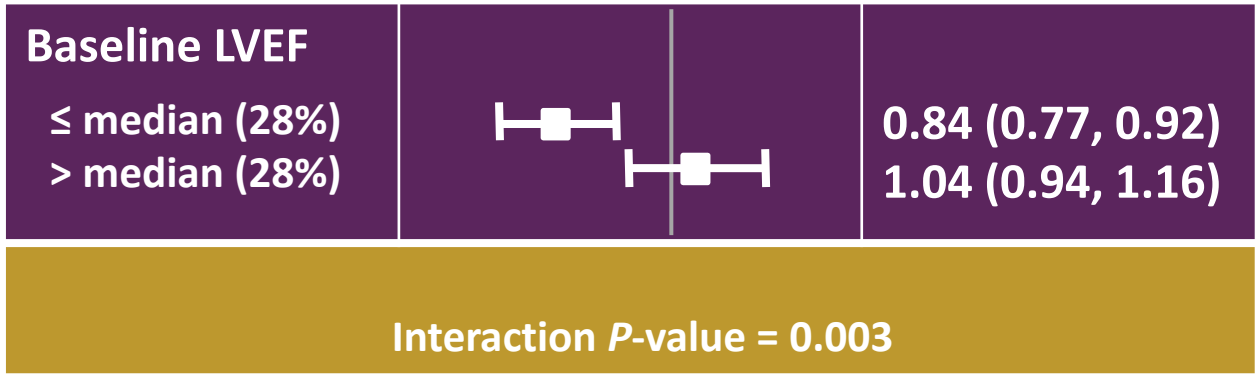
Heterogeneity in Subgroups

Primary Endpoint: CV Death or HFH

VICTORIA



GALACTIC



sick but not too sick?

benefit in LVEF <28 %?

Armstrong P et al. N Engl J Med 2020;382:1883-93.

Teerlink J et al. N Engl J Med 2020; 11/13/2020, *AHA LBCT*

Safety Vericiguat and Omecamtiv

VICTORIA- Vericiguat

- *Trends* for higher risk of symptomatic **hypotension** and syncope
- Higher rates of anemia
- No excess SAE
- **No adverse effects on electrolytes**
- **No adverse effects on renal function**

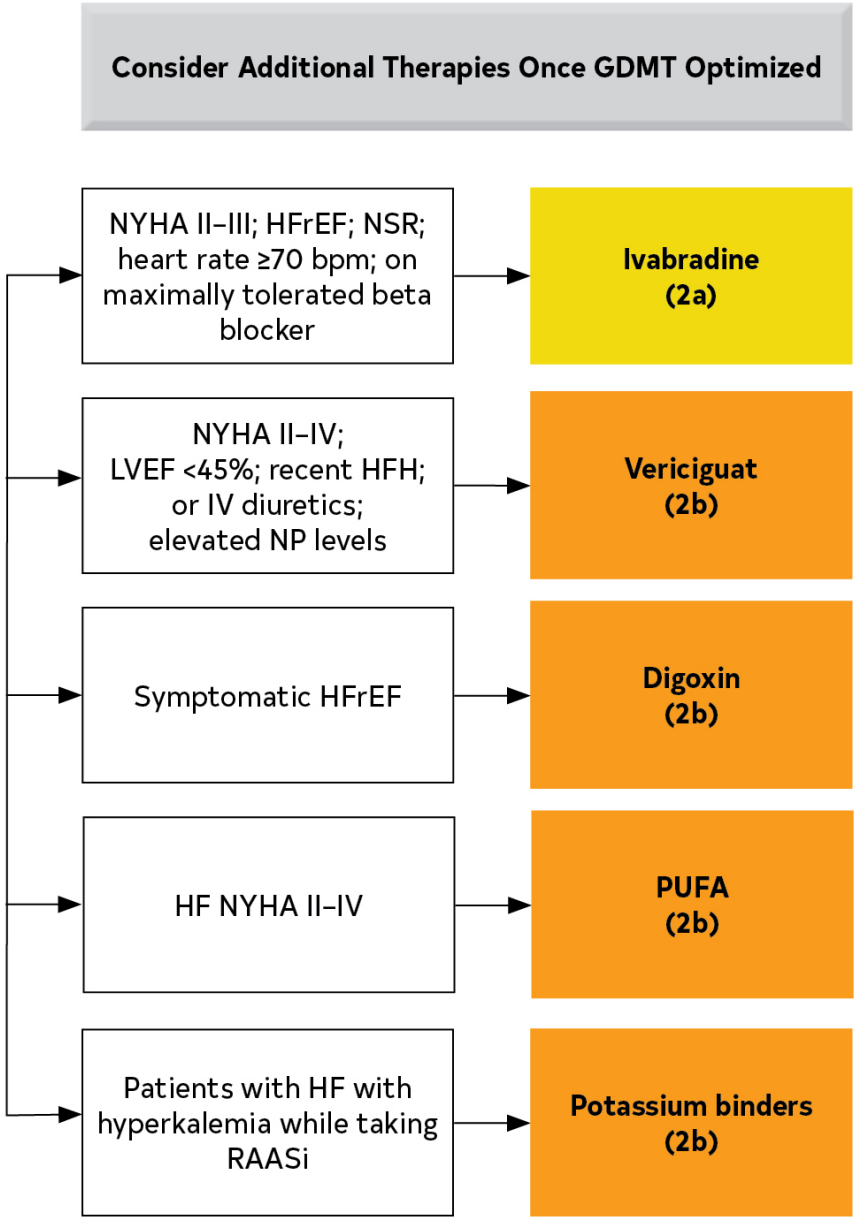
Armstrong P et al. N Engl J Med 2020;382:1883-93.

GALACTIC- Omecamtiv

- No excess risk of symptomatic hypotension
- **No effect on BP**
- No increased risk of myocardial ischemia and ventricular arrhythmias
- No excess risk of SAE
- **Mild rise in troponin I (+0.004 ng/ml)**
- **No adverse effects on electrolytes**
- **No adverse effects on renal function**

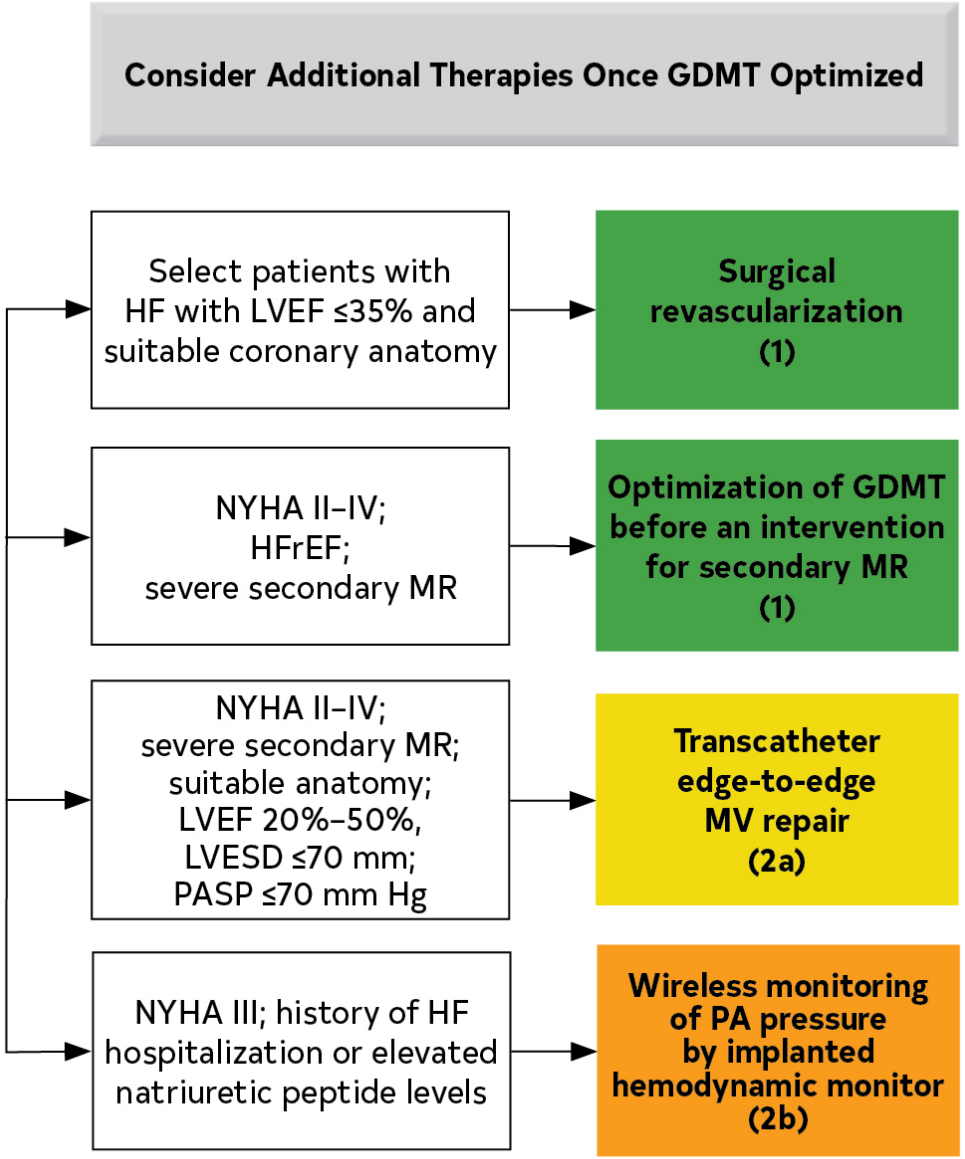
Teerlink J et al. N Engl J Med 2020; 11/13/2020, *AHA LBCT*

Additional Medical Therapies for Patients With HFrEF



Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline

Additional Device Therapies

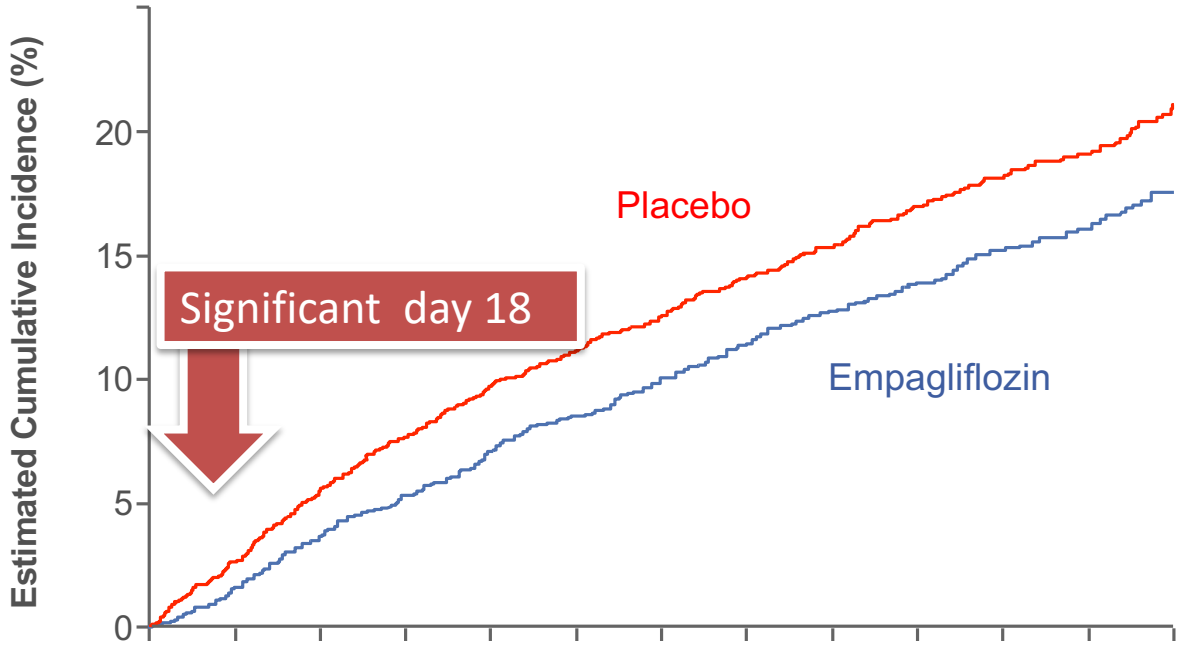


Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline

HFmrEF, HFpEF

HFpEF: EMPEROR-Preserved Trial

~3000 pts NYHA Class II-IV HF, LVEF > 40 % elevated BNP
ARNi (sacubitril valsartan) vs valsartan



HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

RRR 21%

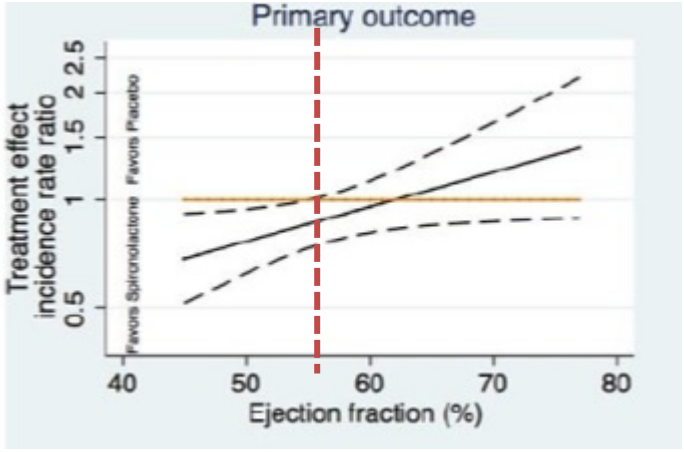
NNT=31

During a median trial period of 26 months.

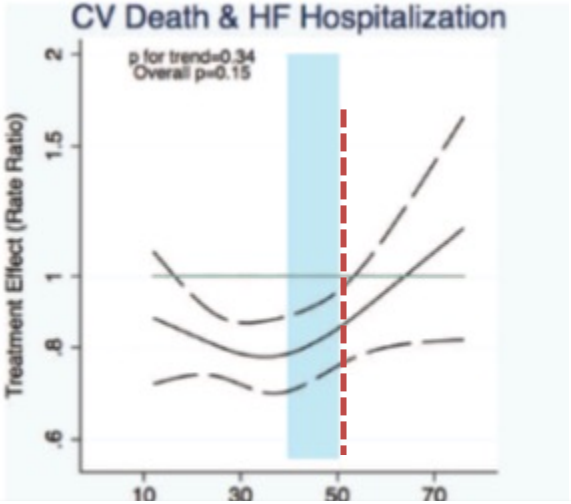
Anker et al NEJM 2021 DOI: 10.1056/NEJMoa2107038

Benefit with ARB, MRA, ARNi, SGLT2i in HFmrEF

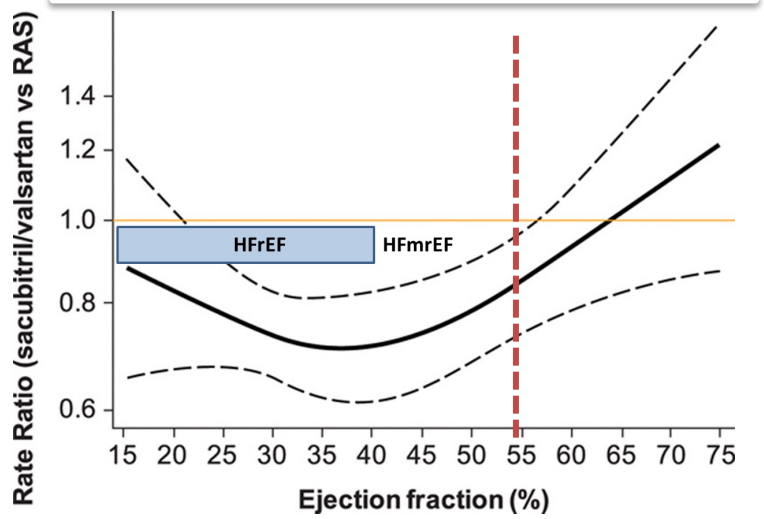
Spironolactone: TOPCAT
Solomon et al, 2016



EHJ ARB: CHARM-PRESERVED
Lund L et al, EJHF, 2018

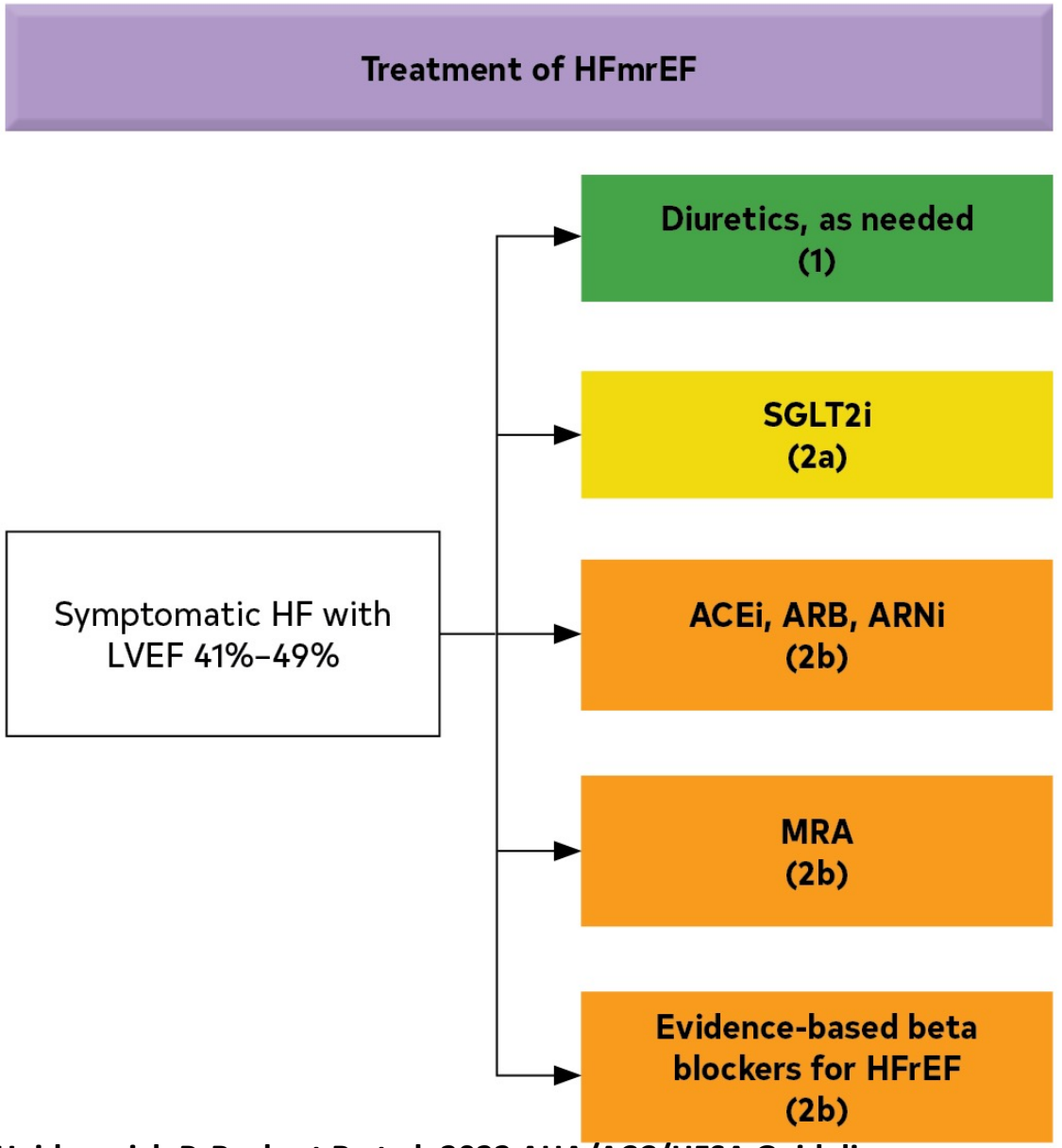


ARNI: PARAGON-HF.
Solomon et al, Circulation, 2020



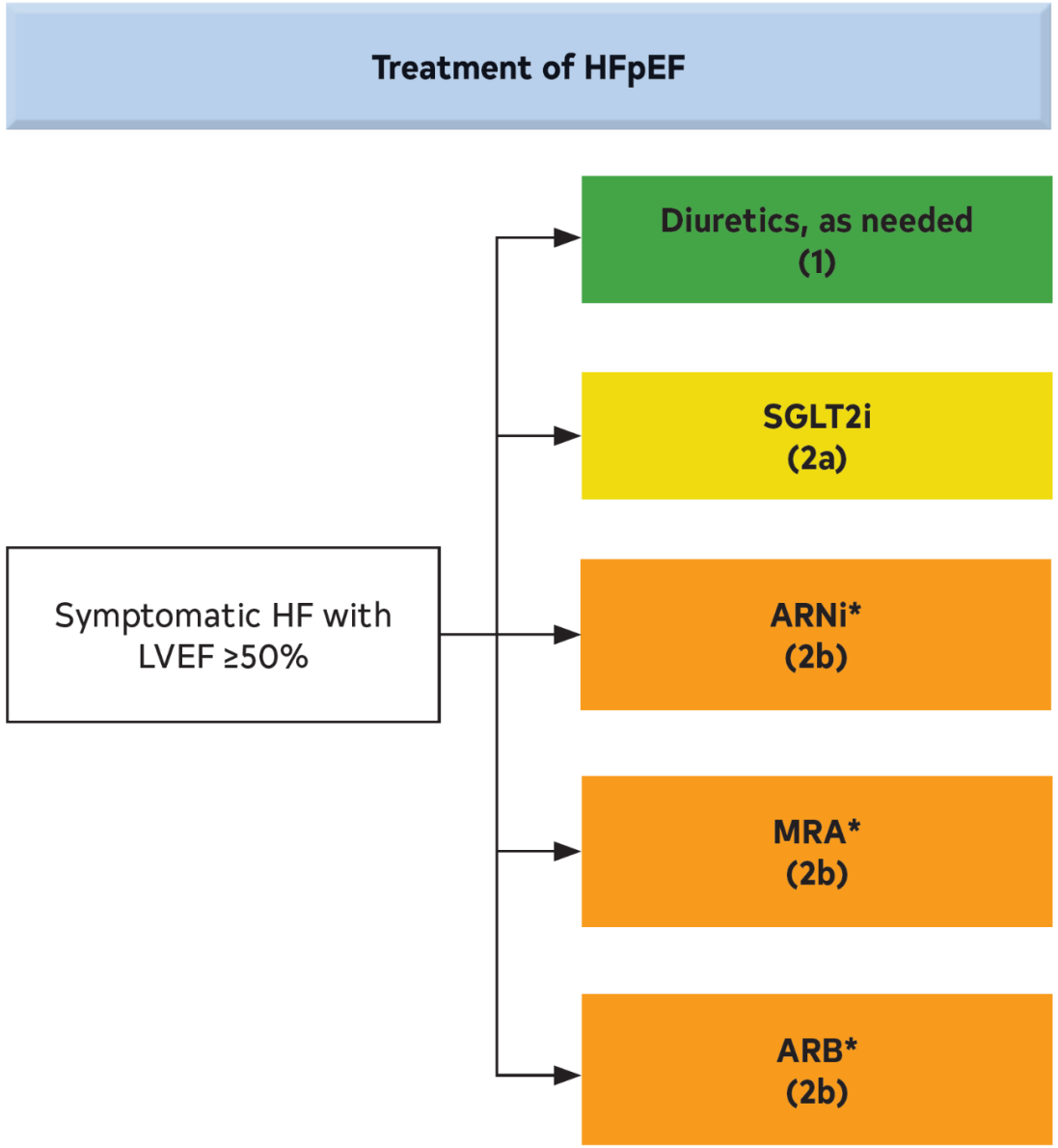
EMPEROR PRESERVED and PARAGON
Packer Circulation. 2021;143:337–349

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



Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline

Recommendations for Patients With Preserved LVEF (≥50%)



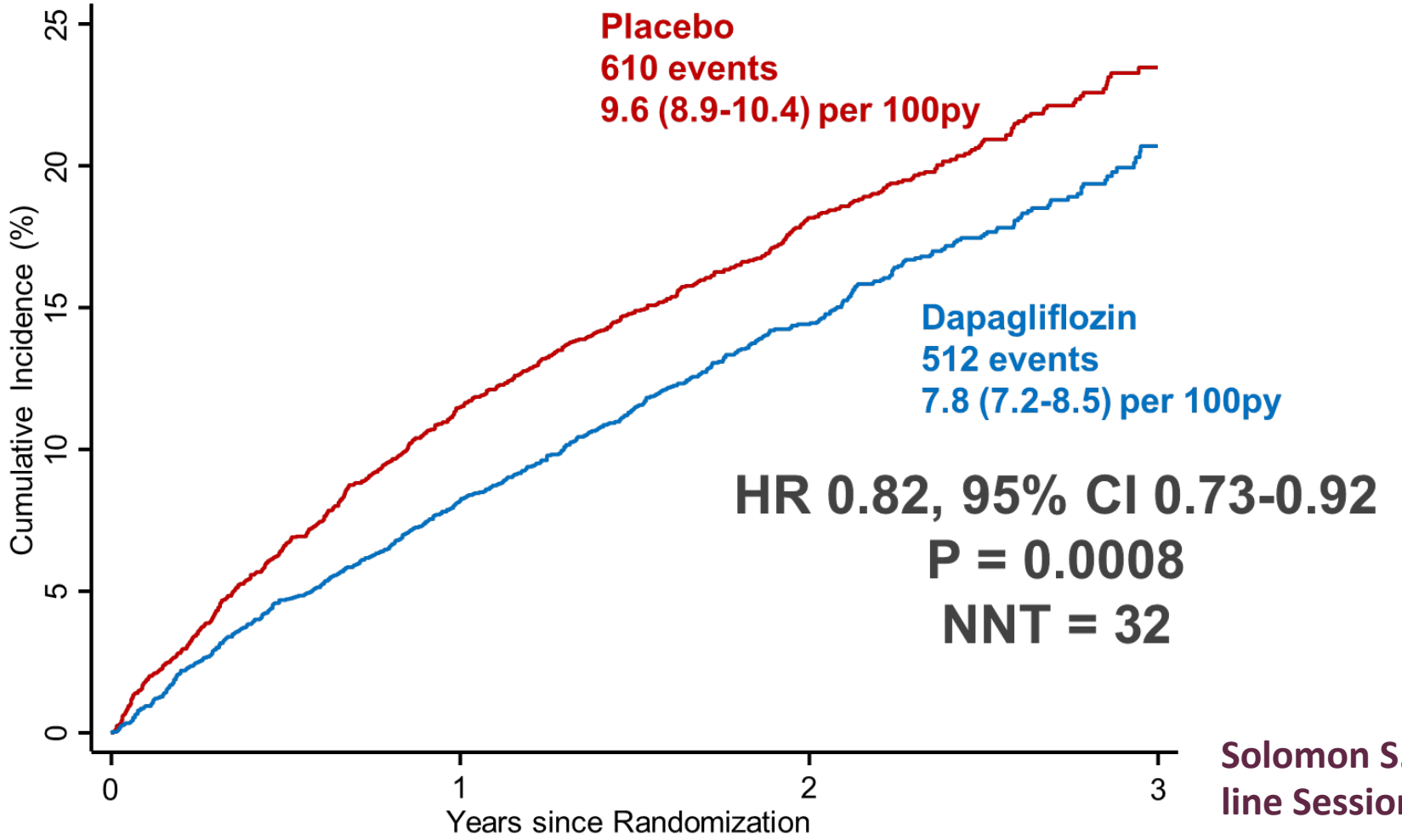
Medication recommendations for HFpEF are displayed.

*Greater benefit in patients with LVEF closer to 50%.

Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline

Recent Results Since Guidelines

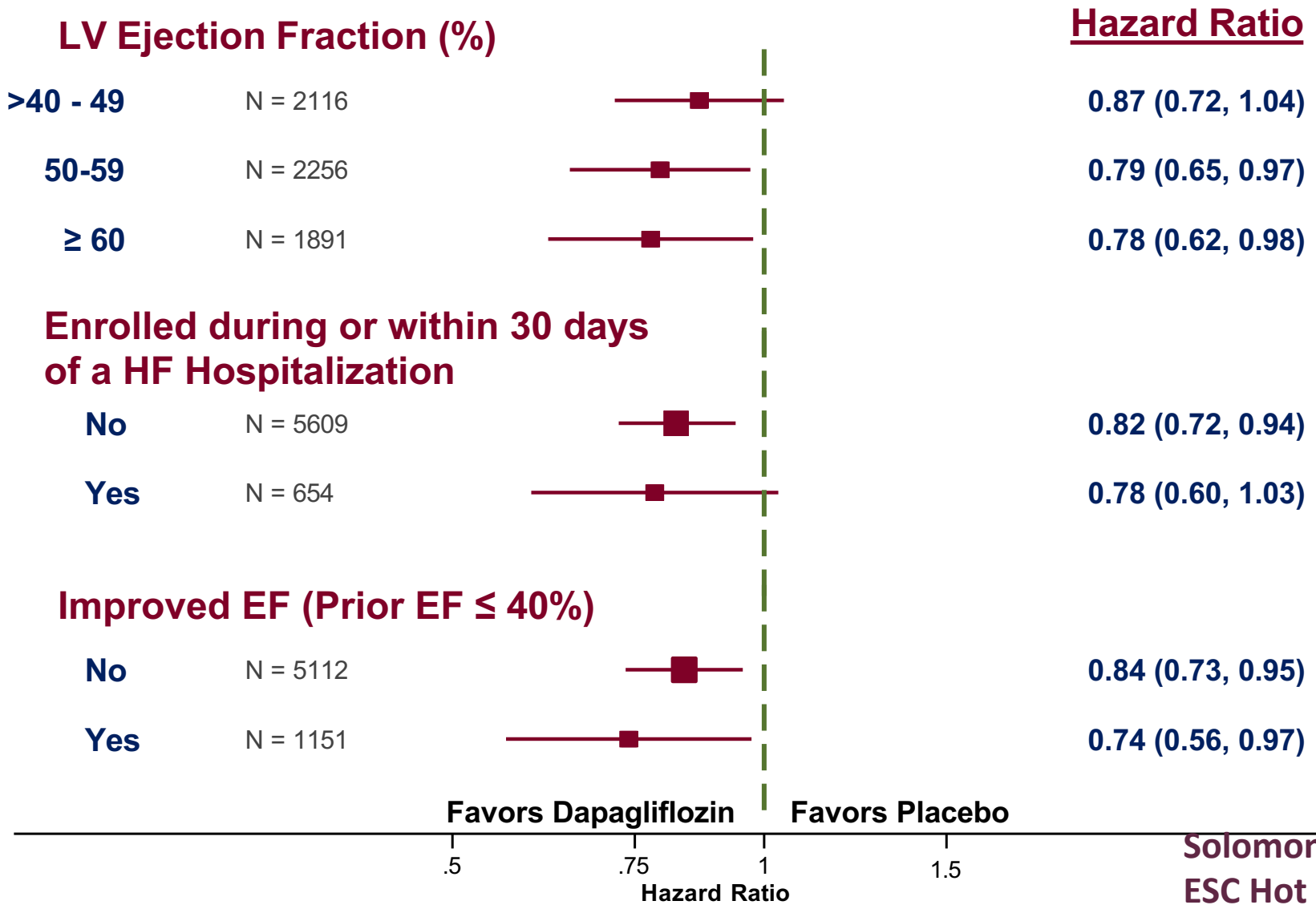
Primary Endpoint: CV Death or Worsening HF



Solomon S. DELIVER ESC Hot line Sessions August 2022

- Largest RCT of **well-treated** patients with **HFmrEF and HFpEF**
- broader population including **HFimpEF (18%), HFmrEF (34%), LVEF 50-59% (36%), LVEF>60% (30%)** and recently hospitalized patients (16% within 3 mo)
- Compared with other recent trials, higher risk: comorbidities, lower LVEF, and higher NT-proBNP levels.

Primary Endpoint in Prespecified Subgroups



Solomon S. DELIVER
ESC Hot line Sessions August 2022

HF With improved Ejection Fraction

Recommendation for HF With Improved Ejection Fraction Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
1	**B-R**	**1. In HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic.**

Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

TRED-HF Trial Conclusions

- Withdrawal of pharmacological HF therapy from patients deemed to have recovered DCM resulted in relapse in ~40% of cases

- Improvement in function represents *remission* rather than *permanent recovery* for many patients

Halliday BP, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2019 Jan 5;393(10166):61-73.

CLINICAL TRAJECTORIES

Other Clinical Trajectory Terminologies in UDHF

New onset/ de novo HF:

- Newly diagnosed HF
- No former history of HF

Worsening HF:

- Worsening symptom/signs/ functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies
- and/or hospitalization

Improving HF:

- Improving symptoms/signs and or functional capacity

Persistent HF:

- Persistent HF with ongoing symptoms/signs and or limited functional capacity

Do not use "Stable HF", instead, use "Persistent"

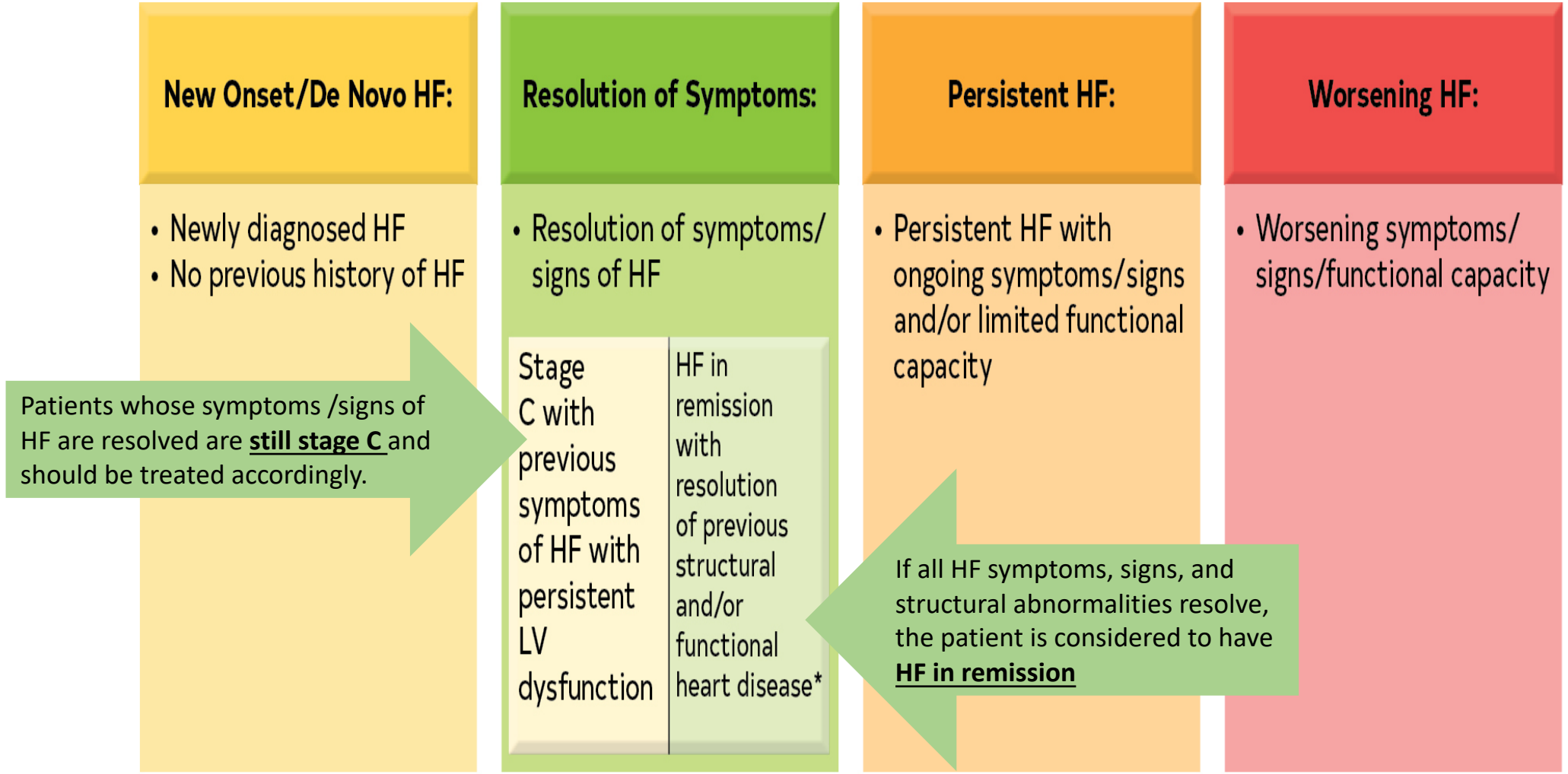
HF in Remission:

- Resolution of symptoms and signs of HF, with resolution of previous structural/functional heart disease after a phase of symptomatic HF

Do not use "Recovered HF" instead, use "HF in Remission"

Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021, ISSN 1071-9164, https://doi.org/10.1016/j.cardfail.2021.01.022.

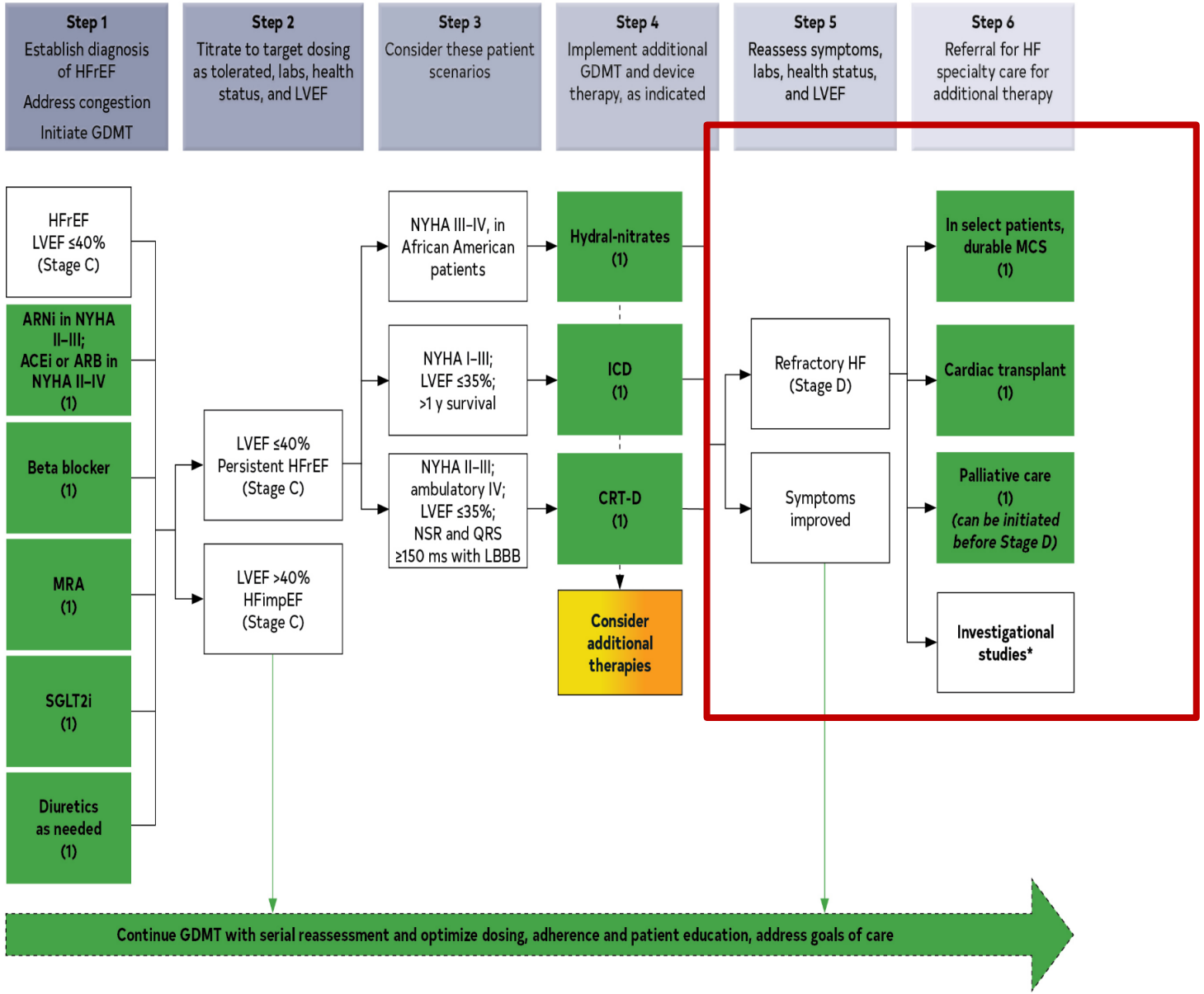
2022 ACC/AHA/HFSA Guidelines Trajectory of Class C HF



Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

Advanced HF Patients

Treatment of HFrEF Stage D



Heidenreich P, Bozkurt B et al. 2022 AHA/ACC/HFSA Guideline, https://doi.org/10.1016/j.jacc.2021.12.012, https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

Recommendation for Specialty Referral to Advanced HF

COR	RECOMMENDATIONS
1	1. In patients with advanced HF, when consistent with the patient's goals of care, timely referral for HF specialty care is recommended to review HF management and assess suitability for advanced HF therapies (e.g., LVAD, cardiac transplantation, palliative care, and palliative inotropes).

Consider if "I-Need-Help" to aid with recognition of patients with advanced HF:

- Complete assessment is not required before referral
- After patients develop end-organ dysfunction or cardiogenic shock, they may no longer quality for advanced therapies

I Intravenous inotropes

E EF ≤35%

E Edema despite escalating diuretics

N New York Heart Association class IIIB or IV, or persistently elevated natriuretic peptides

D Defibrillator shocks

L Low systolic BP ≤90mmHg

E End-organ dysfunction

H Hospitalizations >1

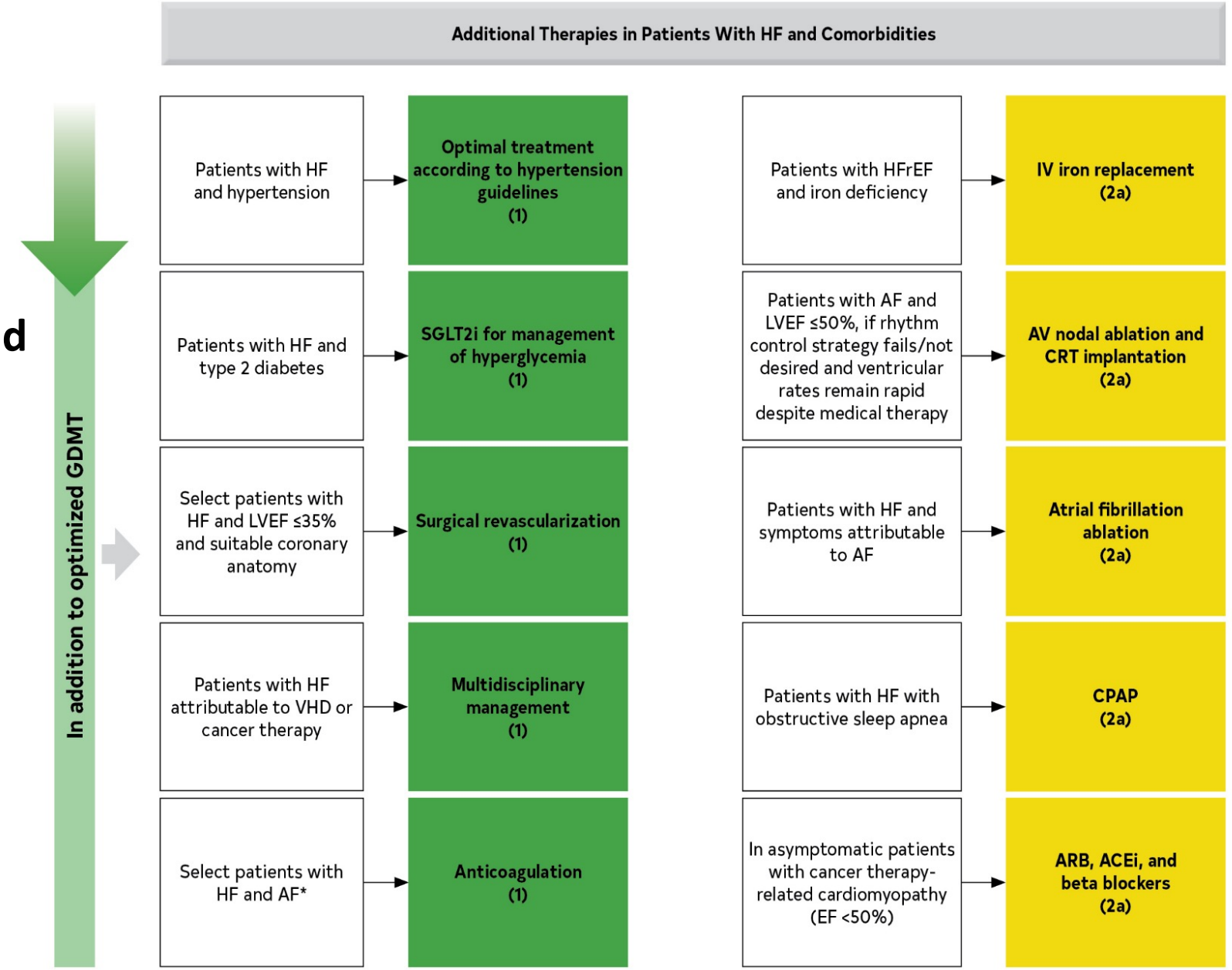
P Prognostic medication; intolerance of GDMT

Abbreviations: BP indicates blood pressure; EF, ejection fraction; GDMT, guideline-directed medical therapy; and LVAD, left ventricular assist device.

American Heart Association.

Treatment of Comorbidities in HF

Recommendations for Treatment of Patients With HF and Selected Comorbidities



Specific Etiology, Specific Populations

HFrEF Stage C- Specific Treatment

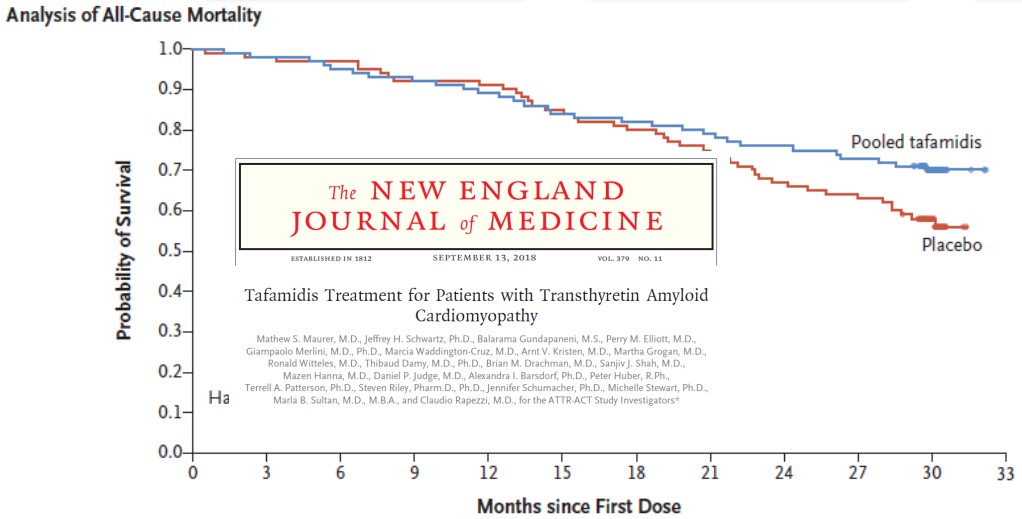
Diagnose and Treat Specific etiology

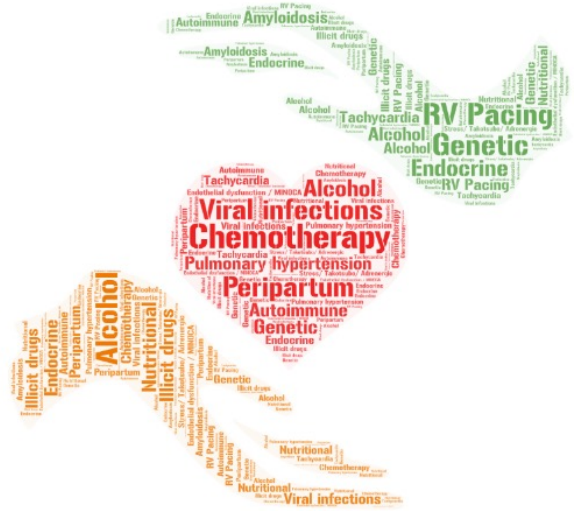
Stage C HFrEF

Treat Specific Etiology

- BB
- ACEi/ARB/ARNi
- MRA
- SGLT2i

- HTN
- Ischemia
- **Amyloidosis**
- Valvular Heart disease
- **Chemotherapy** , immunomodulators
- **COVID-19**, Viral
- Illicit Drugs / ETOH
- Takotsubo/Tachycardia
- Metabolic
- MINOCA /Microvascul.
- RVF, PAH, RV Pacing
- Genetic
- Peripartum





Maurer et al.N Engl J Med 2018; 379:1007-1016

Modified from Bozkurt et al. Circulation. 2016 Dec 6;134(23):e579-e646

Summary: 2022 HF Guidelines

HFrEF

COR	LOE	
1	A	In patients with HFrEF, ARNi or ACEi/ARB, SGLT2i, BB, MRA are recommended to reduce morbidity and CV mortality

HFmrEF

2a	B-R	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HFH and cardiovascular mortality
2b	B-NR	Among patients with symptomatic HFmrEF, use of BB, ARNi, ACEi or ARB, and MRAs may be considered to reduce the risk of HFH and CV mortality, particularly among patients with LVEF on the lower end of this spectrum.

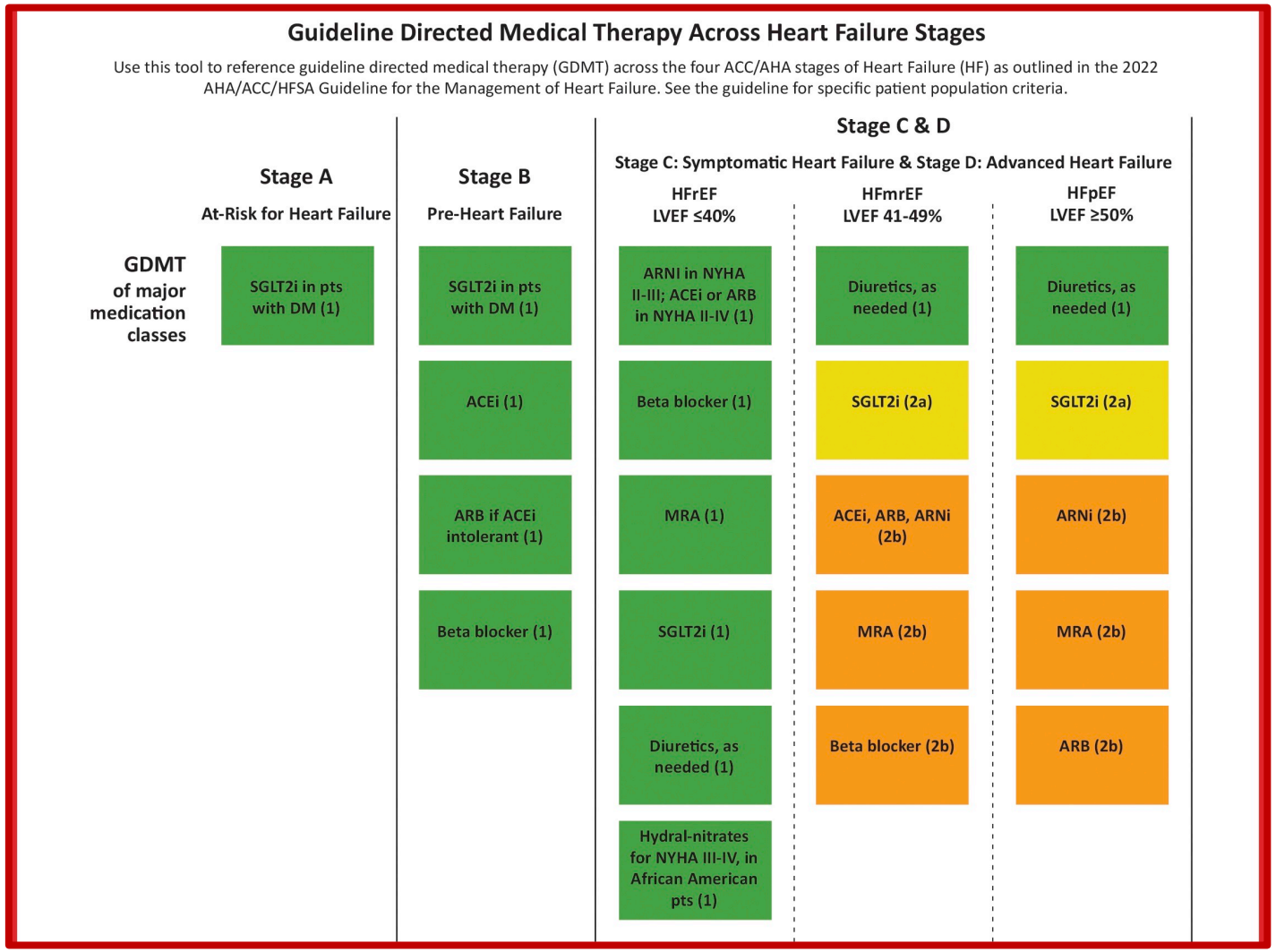
HFpEF

2a	B-R	In patients with HFpEF, SGLT2i can be beneficial in decreasing HFH and cardiovascular mortality
2b	B-NR	In selected patients with HFpEF, MRA, ARB, or ARNi may be considered to decrease hospitalizations particularly among patients with LVEF on the lower end of this spectrum.

HFimpEF

1	B-R	In HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic.

Summary: Treatment Across Stages of HF: At risk, Pre-HF, HF to Advanced HF



Summary: UDHF Definitions and Classification

Standardization of HF syndrome definition

Symptoms / signs caused by a structural / functional cardiac abnormality and corroborated by *at least one* of the following:

- elevated NP levels
- objective evidence of congestion by diagnostic modalities

- to enhance appropriate diagnosis and optimization of GDMT
- achieve uniformity of care

New revised classification of HF

- **At Risk for HF,**
- **Pre-HF**
- **HF**
- **Advanced HF**

Easy to understand by patients and clinicians

Clarify treatment indications for pre-HF as well as HF

EF Classifications

HFrEF: LVEF ≤ 40%
HFmrEF : LVEF 41-49%
HFpEF: LVEF ≥ 50%
HFimpEF: LVEF ≤ 40%, ≥ 10 point ↑, subsequent LVEF>40%

Standardization & clarity for treatment indications

Emphasis for improved, not recovered EF

Trajectories

Persistent HF rather than stable HF

HF in remission rather than recovered HF

Summary:

- Heart failure is preventable
- Heart failure is treatable
- Heart failure course can be changed
- There are significant advances in HF treatment that result in improvement in clinical outcomes, hospitalization rates, quality of life and improvement in LV Function
- It is critical for HF patients to have access to health care and receive timely treatment

~~Heart Failure~~