

Updates in the Management of Heart Failure with Reduced Ejection Fraction

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Advanced Heart Failure and Cardiac Transplant

1/31/2026

UNIVERSITY *of* WASHINGTON



Case Presentation

47 year old man who presented to the Emergency Department with shortness of breath

- HPI
 - Notes worsening shortness of breath over the course of 3 weeks prior to presentation
 - Notes increasing lower extremity edema and increasing difficulty laying flat to sleep
- PMH
 - Hypertension
 - Diabetes mellitus (HbA1c 7.1)
 - Dyslipidemia

Case Presentation

Vitals

BP: 134/85 P: 100 SpO2: 93%

Admission Labs

Sodium	138	135 - 145 meq/L
Potassium	4.9	3.6 - 5.2 meq/L
Chloride	103	98 - 108 meq/L
Carbon Dioxide, Total	25	22 - 32 meq/L
Anion Gap	10	4 - 12
Glucose	100	62 - 125 mg/dL
Urea Nitrogen	15	8 - 21 mg/dL
Creatinine	0.56	0.38 - 1.02 mg/dL
Protein (Total)	7.5	6.0 - 8.2 g/dL
Albumin	4.3	3.5 - 5.2 g/dL
Bilirubin (Total)	0.4	0.2 - 1.3 mg/dL
Calcium	9.5	8.9 - 10.2 mg/dL
AST (GOT)	23	9 - 38 U/L
Alkaline Phosphatase (Total)	140 (H)	31 - 132 U/L
ALT (GPT)	39 (H)	7 - 33 U/L
eGFR by CKD-EPI 2021	>60	>59 mL/min/1.73_m2

WBC	13.30 (H)	4.3 - 10.0 10 ³ /uL
RBC	5.84 (H)	3.80 - 5.00 10 ⁶ /uL
Hemoglobin	17.3 (H)	11.5 - 15.5 g/dL
Hematocrit	53 (H)	36.0 - 45.0 %
MCV	91	81 - 98 fL
MCH	29.6	27.3 - 33.6 pg
MCHC	32.5	32.2 - 36.5 g/dL
Platelet Count	306	150 - 400

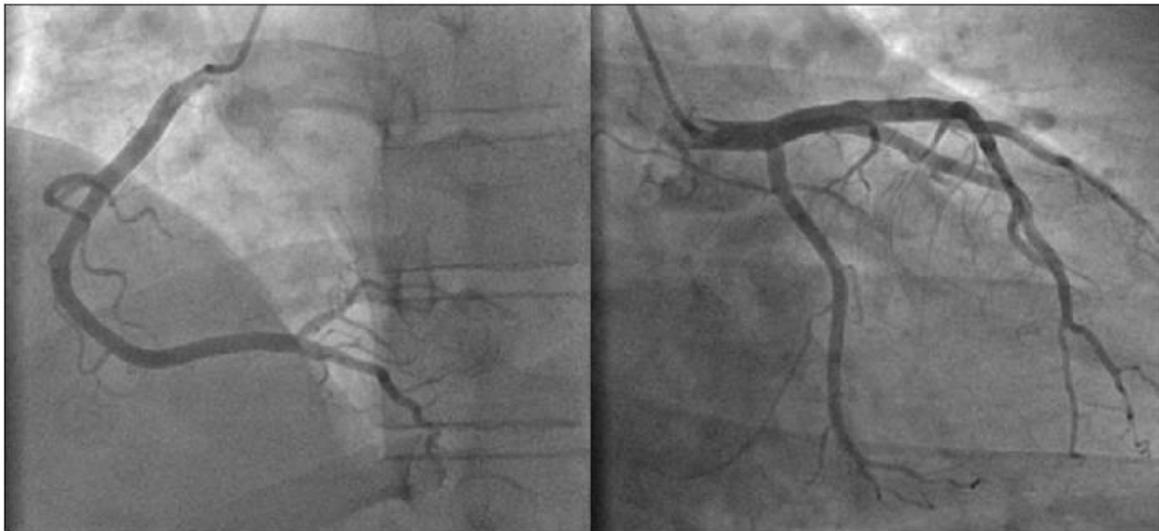
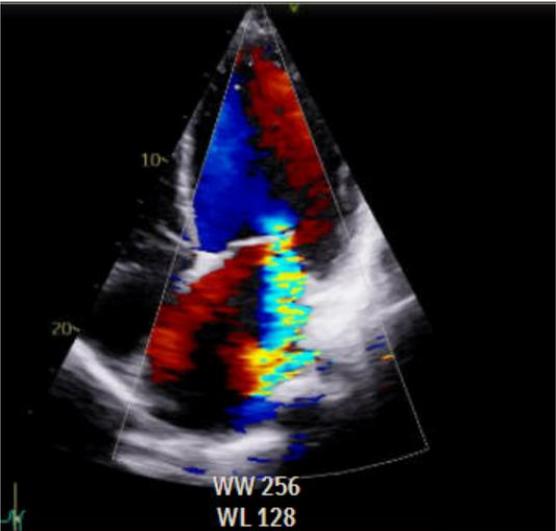
BNP: >700

Case Presentation



Transthoracic echocardiogram

- Left ventricular dysfunction with estimated LVEF approximately 30-35%
- At least moderate mitral regurgitation
- Mild right ventricular dilatation



Coronary angiography

- Normal coronary anatomy

Case Presentation

He is started on IV diuretics and transitioned to oral diuretics. He is discharged on the following medications:

- Losartan 25 mg daily
- Spironolactone 12.5 mg daily
- Metoprolol succinate 25 mg daily
- Furosemide 40 mg daily

He is now following up with in the office one week after discharge. What would be the next best step in his management?

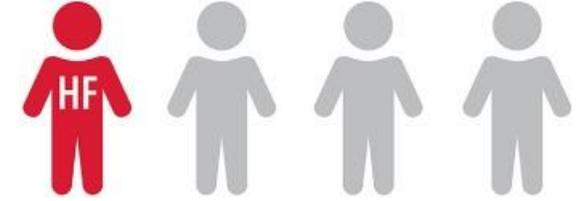
- A) Attempt to further optimize his medical therapy
- B) Refer for primary prevention implantable cardioverter-defibrillator
- C) Refer for transplant/LVAD evaluation
- D) Nothing- monitor his progress and his symptoms

Agenda

- > **Heart Failure Epidemiology**
- > **Updated Definition of Heart Failure**
- > **Pathophysiology of Heart Failure with Reduced Ejection Fraction (HFrEF)**
- > **Medical Therapy for HFrEF**
- > **New Innovations**
- > **Summary**

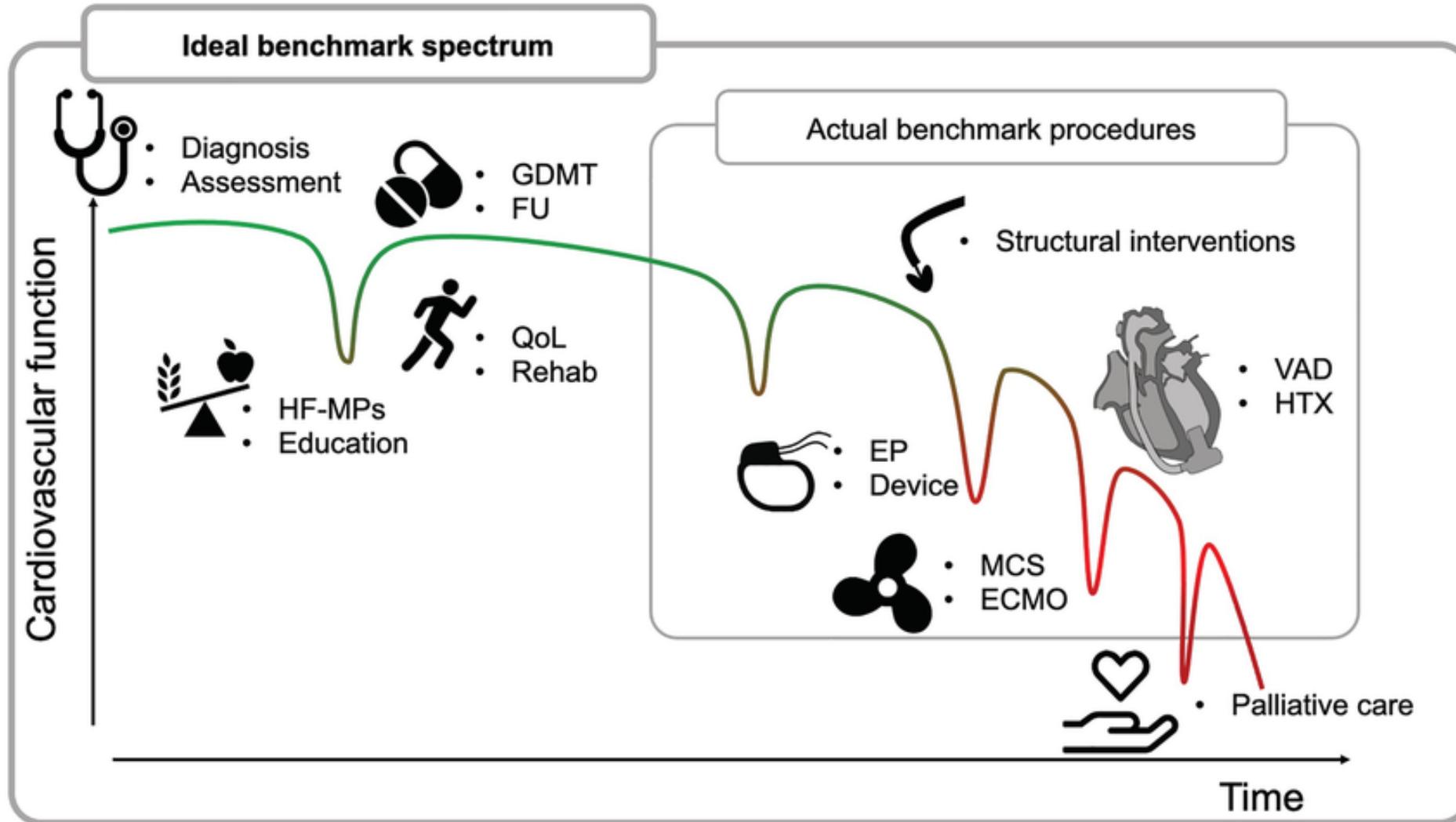


Heart Failure by Numbers



- Approximately 6.7 million Americans over 20 years old carry a diagnosis of heart failure. With expected projections of:
 - 8.7 million in 2030
 - 10.3 million in 2040
 - 11.4 by 2050
- In 2020, it was estimated that HF was responsible for 32 billion in direct costs and an additional 14 billion in indirect costs
- Lifetime risk of HF has increased to 24%- approximately 1 in 4 Americans will develop heart failure in their lifetime
- Heart failure mortality rates have been increasing since 202 with heart failure accounted for 45% of cardiovascular deaths in 2021
 - Among patients 65 years and older, patients who have been hospitalized with heart failure have an estimated mortality rate of 35% at 1 year post discharge
- In 2021 there was 1.2 million primary HF hospitalizations

Why do we care about Heart Failure?



1- Year Mortality

Stage A: 2-3%

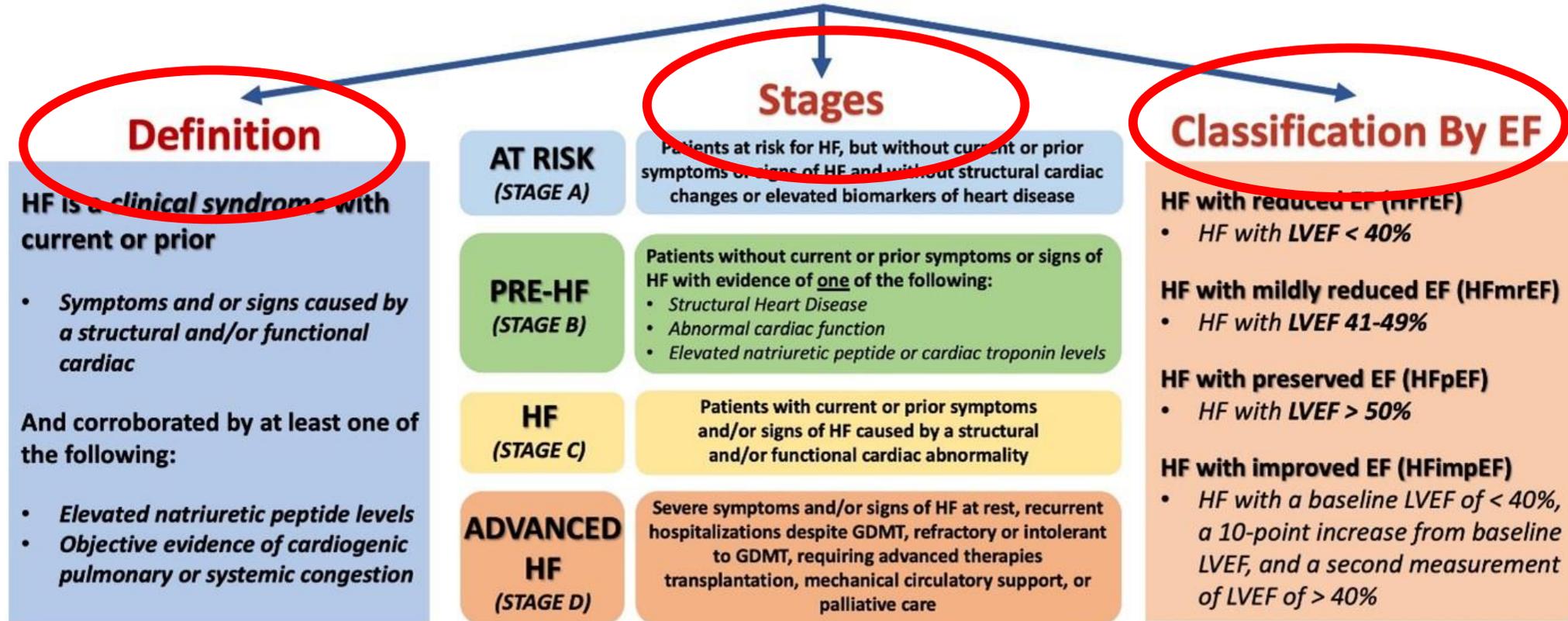


Stage D: >50%

This mortality rate is IRRESPECTIVE of ejection fraction

Defining of Heart Failure

Universal Definition and Classification of Heart Failure (HF)



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.”

Defining of Heart Failure

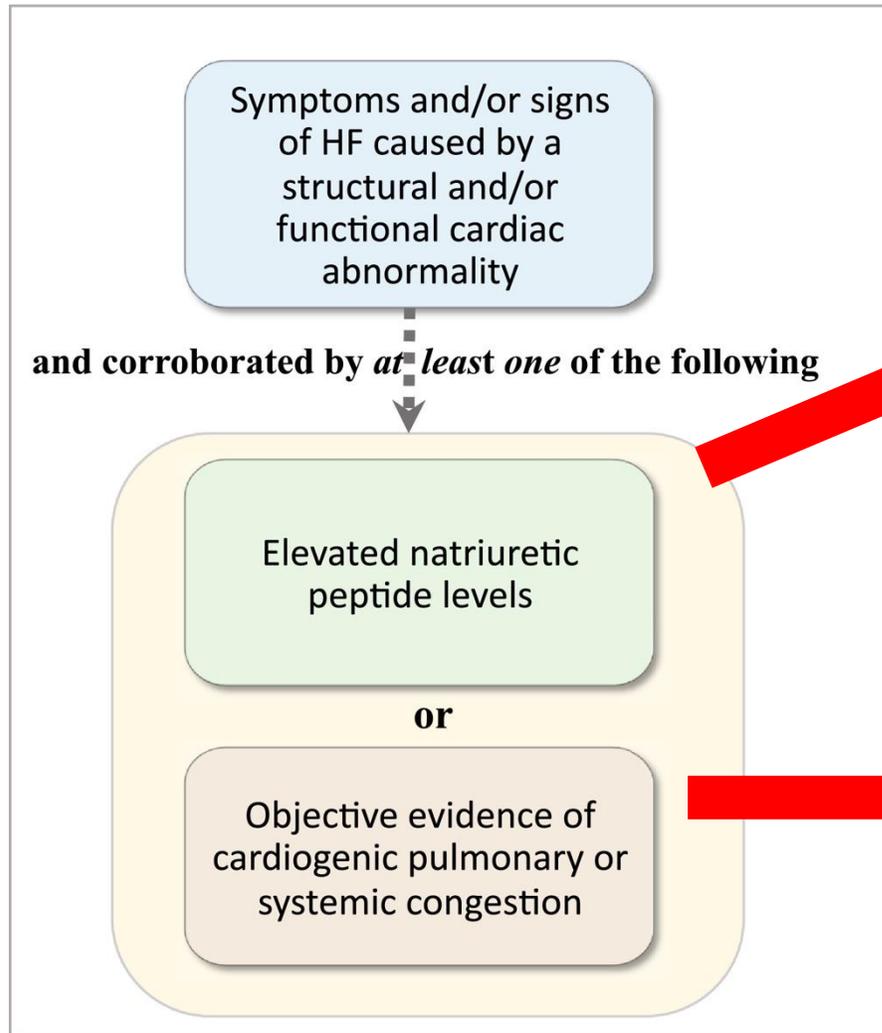
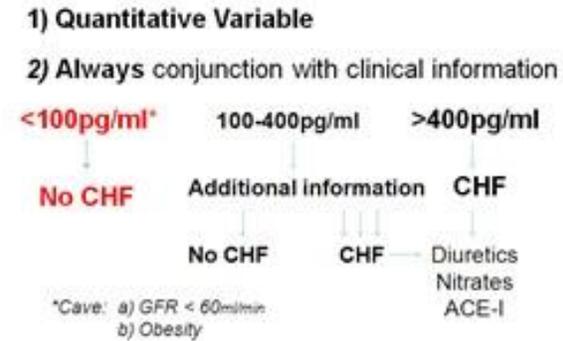
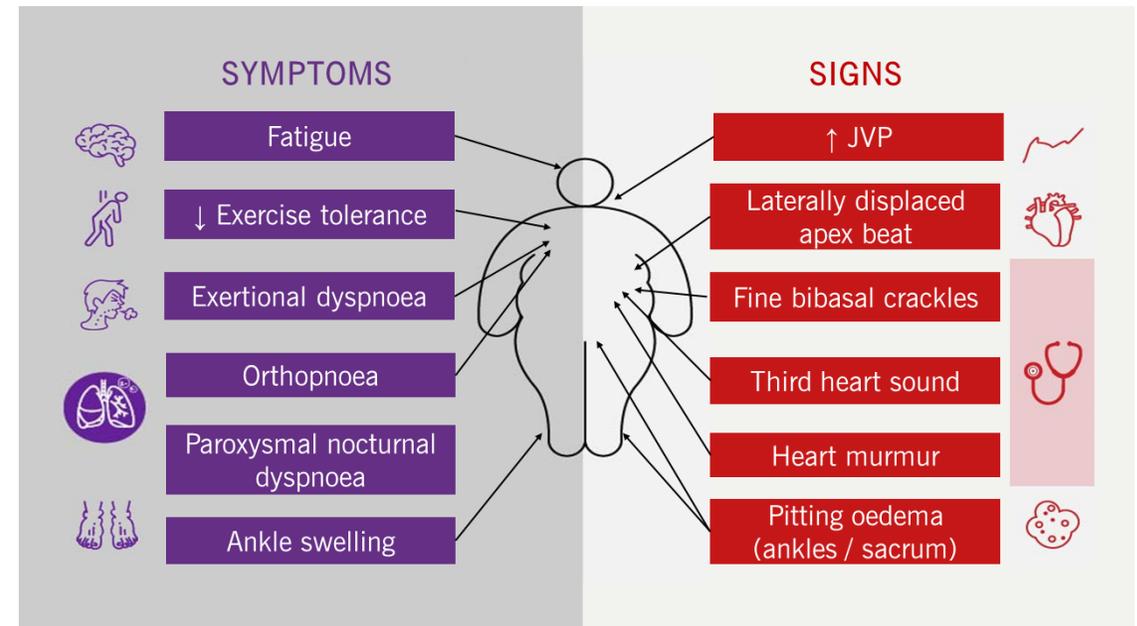


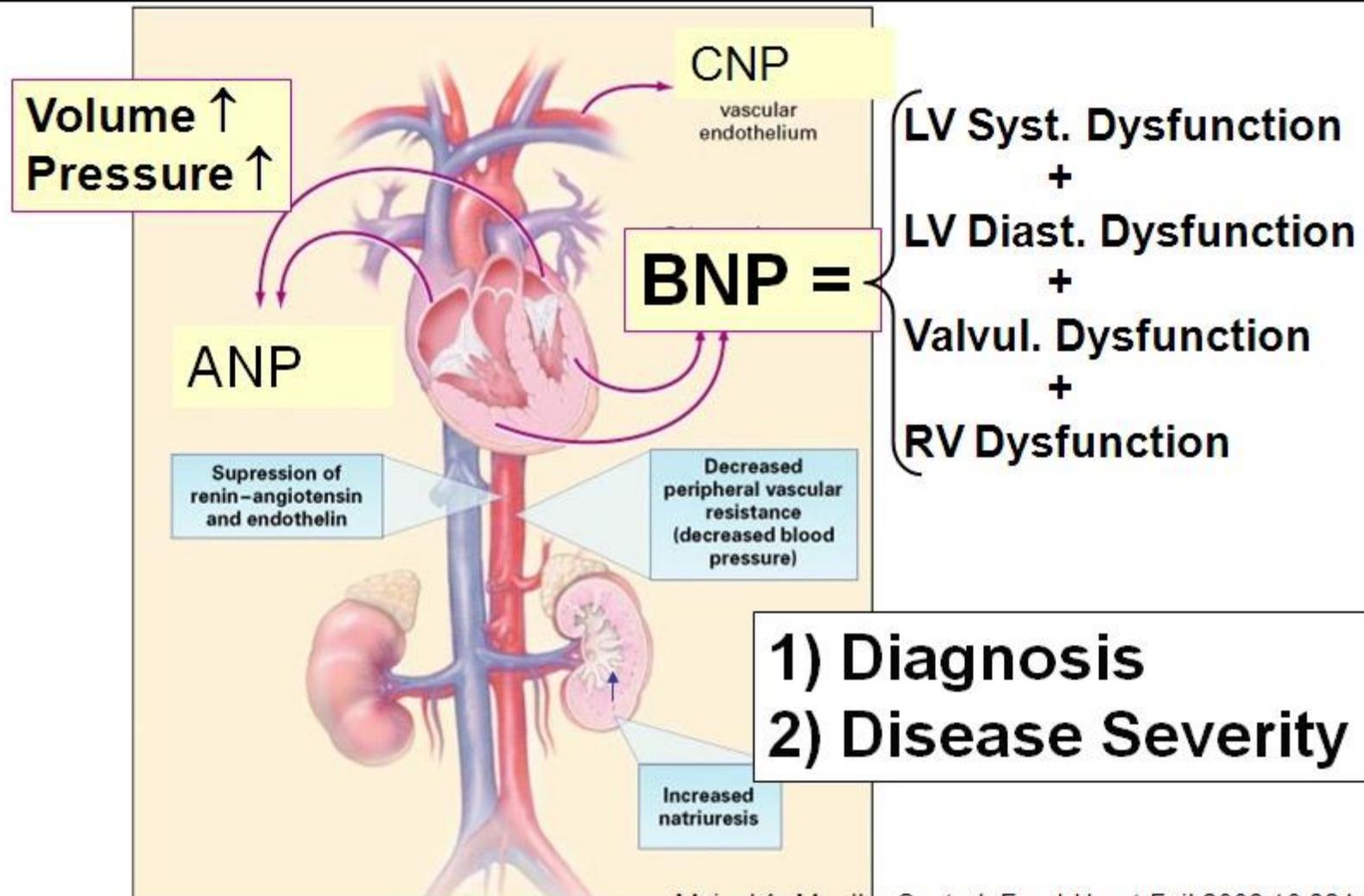
FIGURE 3
Interpretation of BNP in Acute Dyspnea

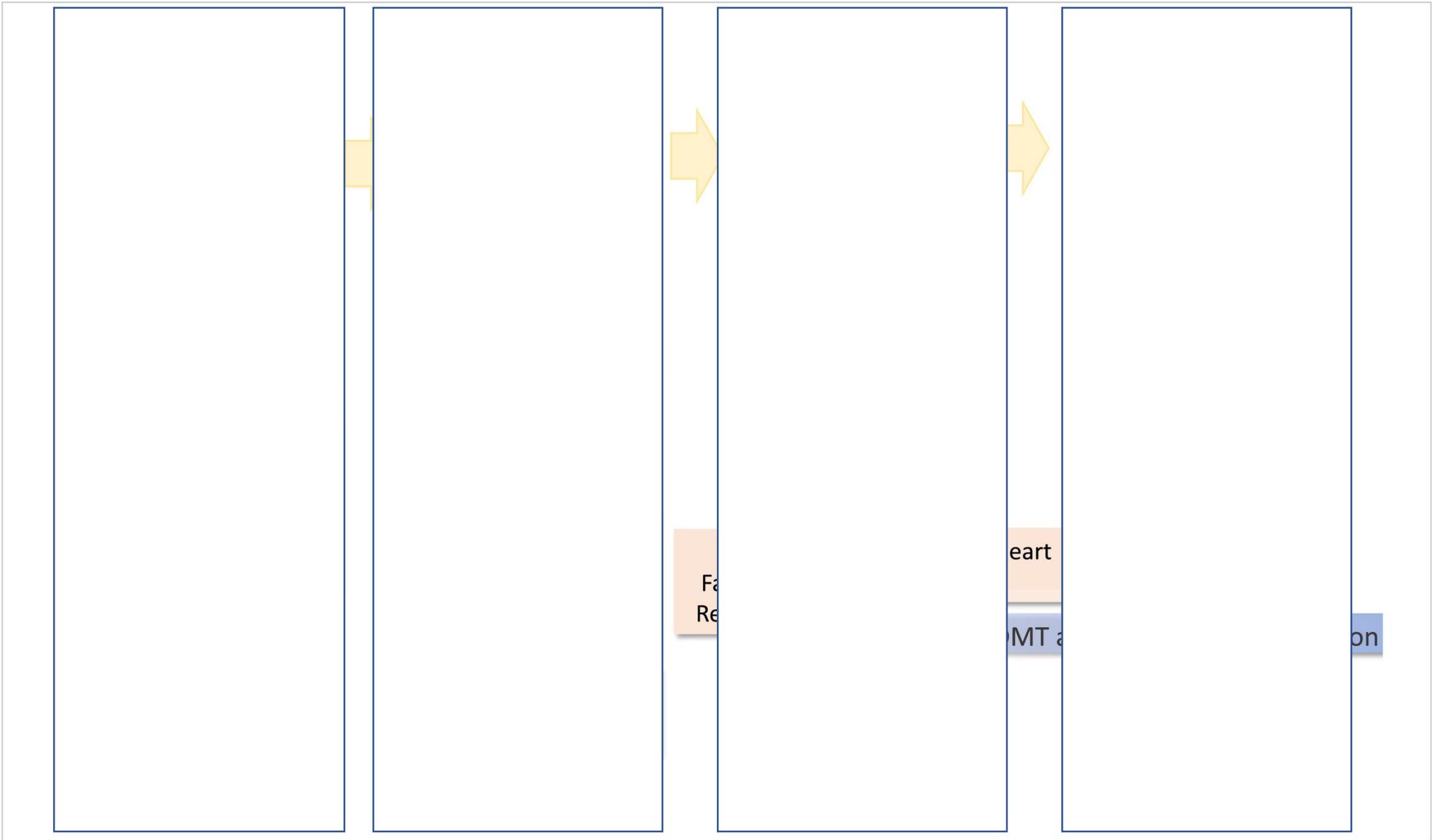


Marcel A. Mueller C, et al. Eur J Heart Fail 2008;10:824-30



NP: Marker of Cardiac Stress





Fa
Re

heart
MT a

on

HF with reduced EF (HFrEF):

- HF with LVEF $\leq 40\%$

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%

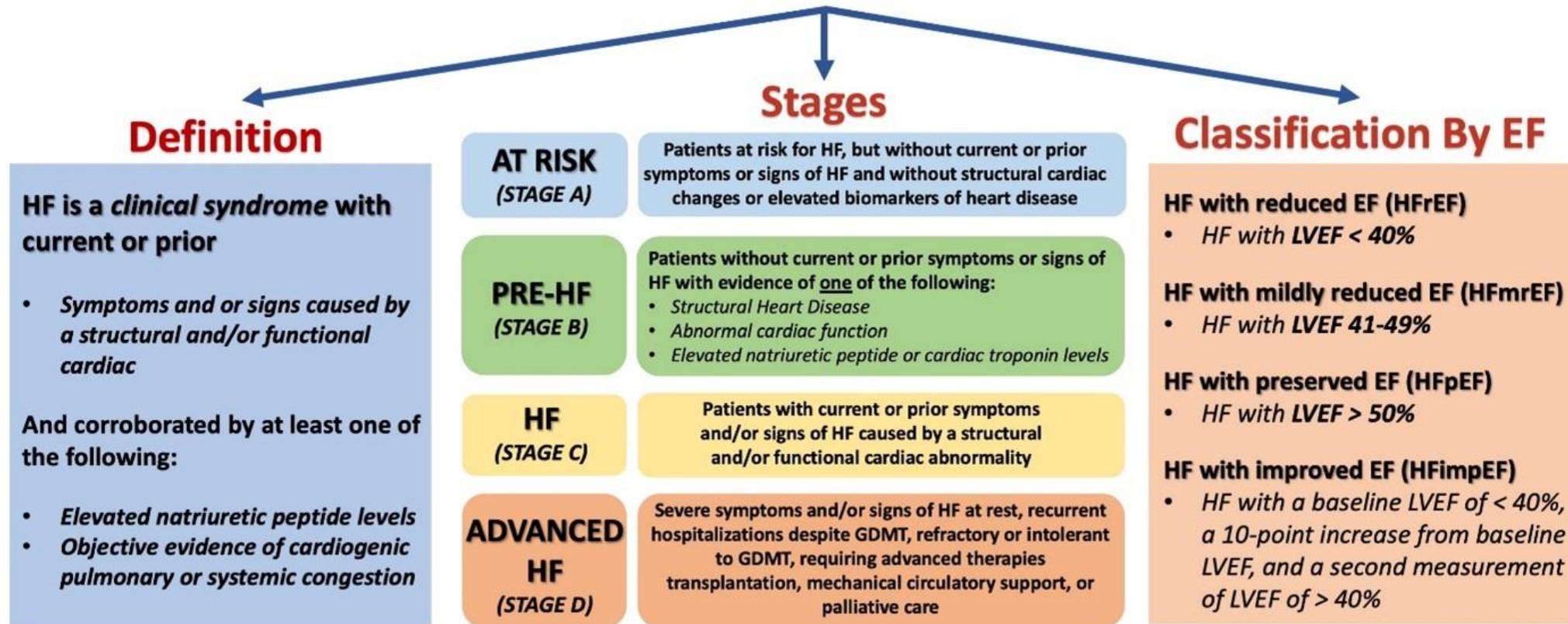
HF with preserved EF (HFpEF):

- HF with LVEF $\geq 50\%$

HF with improved EF (HFimpEF):

- HF with a baseline LVEF $\leq 40\%$, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF $> 40\%$

Universal Definition and Classification of Heart Failure (HF)



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.”

*The spectrum of HFmEF:
A continuum of disease*

HFrEF

HFmEF

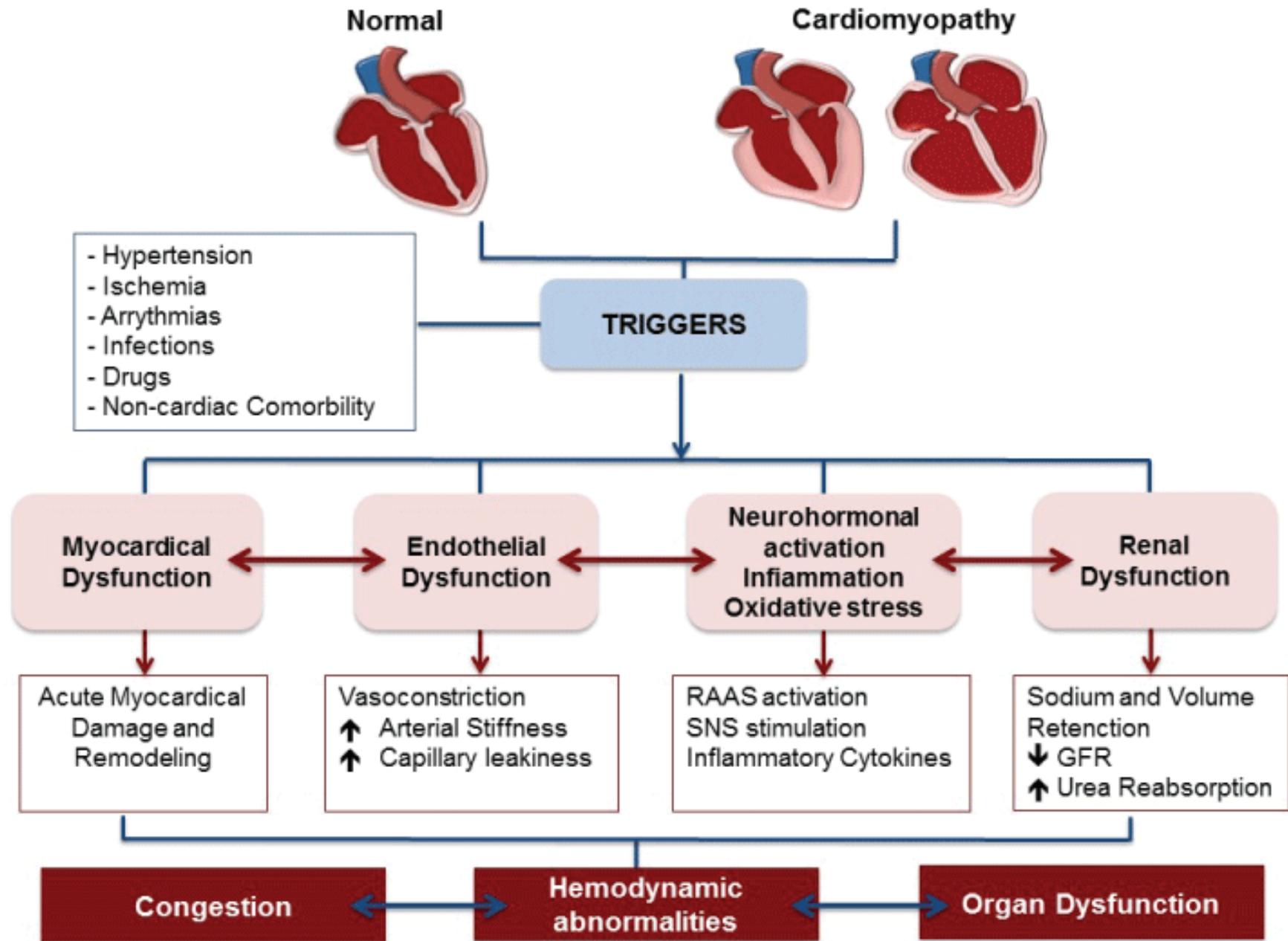
HFpEF

**Male, younger age, diabetes,
CAD, CMD, CKD, cardiac comorbidities**

**Female, older age, ↑BMI, AF, hypertension ,
extra cardiac comorbidities, Metabolic diseases
Mitral valve defects**



CAD Coronary Artery Disease; CMD dilated cardiomyopathy CKD Chronic Kidney Disease; BMI Body Mass Index; AF Atrial Fibrillation



What causes heart failure?

- Heart failure is the end stage manifestation of most forms of heart disease
- The role that coronary artery disease plays in the development of heart failure is evolving
- Traditional risk factors also play a role in the development of heart failure
 - Hypertension
 - Diabetes
 - Dyslipidemia
 - Smoking

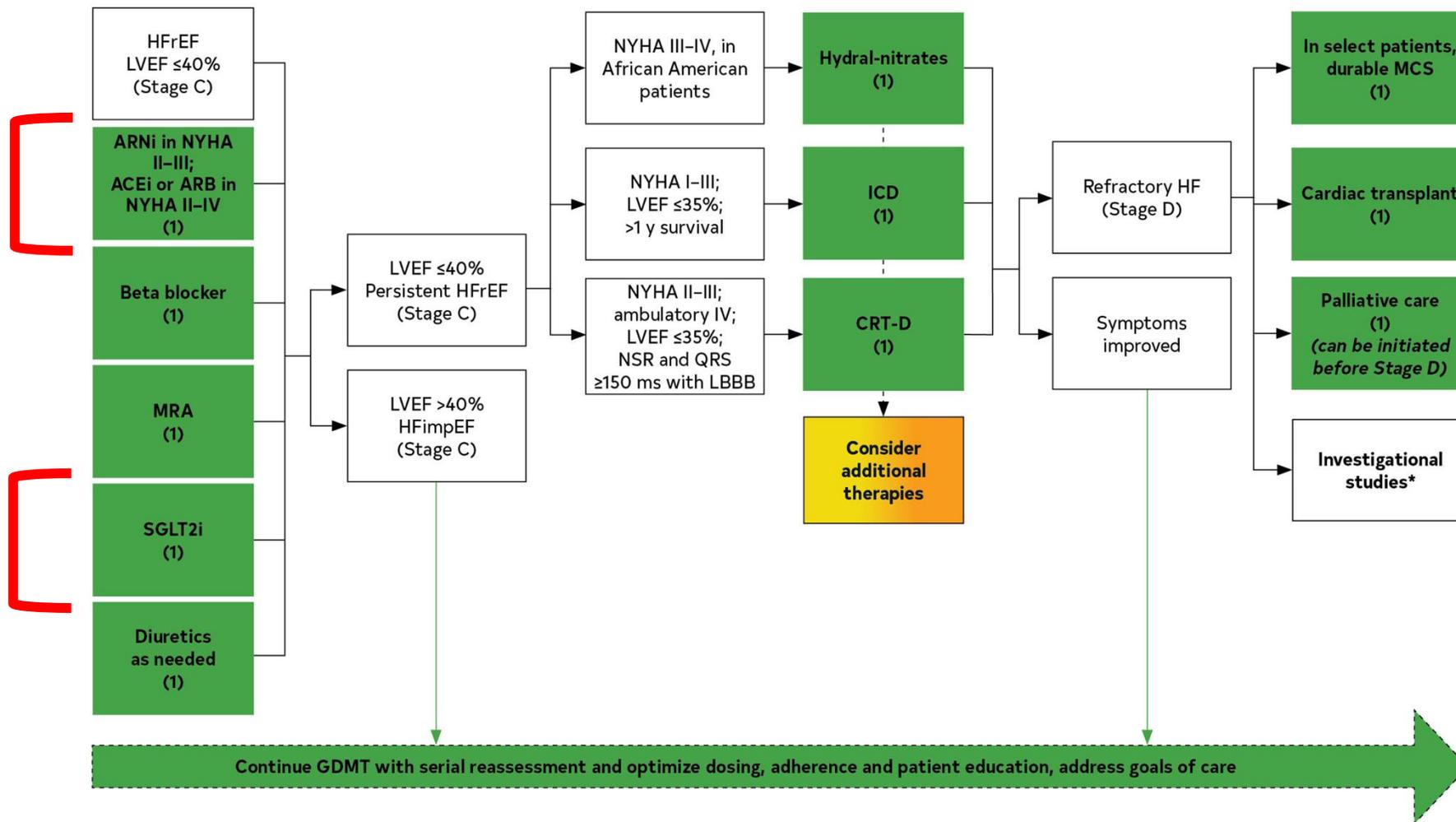
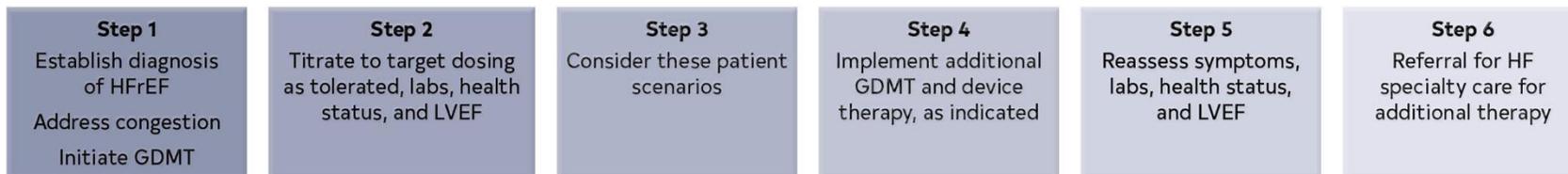
What's Changed in Managing Heart Failure?



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Paul A. Heidenreich, MD, MS, FACC, FAHA, HFSA, Chair, Biykem Bozkurt, MD, PhD, FACC, FAHA, HFSA, Vice Chair, David Aguilar, MD, MSc, FAHA, Larry A. Allen, MD, MHS, FACC, FAHA, HFSA, Joni J. Byun, Monica M. Colvin, MD, MS, FAHA, Anita Deswal, MD, MPH, FACC, FAHA, HFSA, Mark H. Drazner, MD, MSc, FACC, FAHA, HFSA, Shannon M. Dunlay, MD, MS, FAHA, HFSA, Linda R. Evers, JD, James C. Fang, MD, FACC, FAHA, HFSA, Savitri E. Fedson, MD, MA, Gregg C. Fonarow, MD, FACC, FAHA, HFSA, Salim S. Hayek, MD, FACC, Adrian F. Hernandez, MD, MHS, Prateeti Khazanie, MD, MPH, HFSA, Michelle M. Kittleson, MD, PhD, Christopher S. Lee, PhD, RN, FAHA, HFSA, Mark S. Link, MD, Carmelo A. Milano, MD, Lorraine C. Nnacheta, DrPH, MPH, Alexander T. Sandhu, MD, MS, Lynne Warner Stevenson, MD, FACC, FAHA, HFSA, Orly Vardeny, PharmD, MS, FAHA, HFSA, Amanda R. Vest, MBBS, MPH, HFSA, and Clyde W. Yancy, MD, MSc, MACC, FAHA, HFSA [SHOW](#)

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Targeted doses

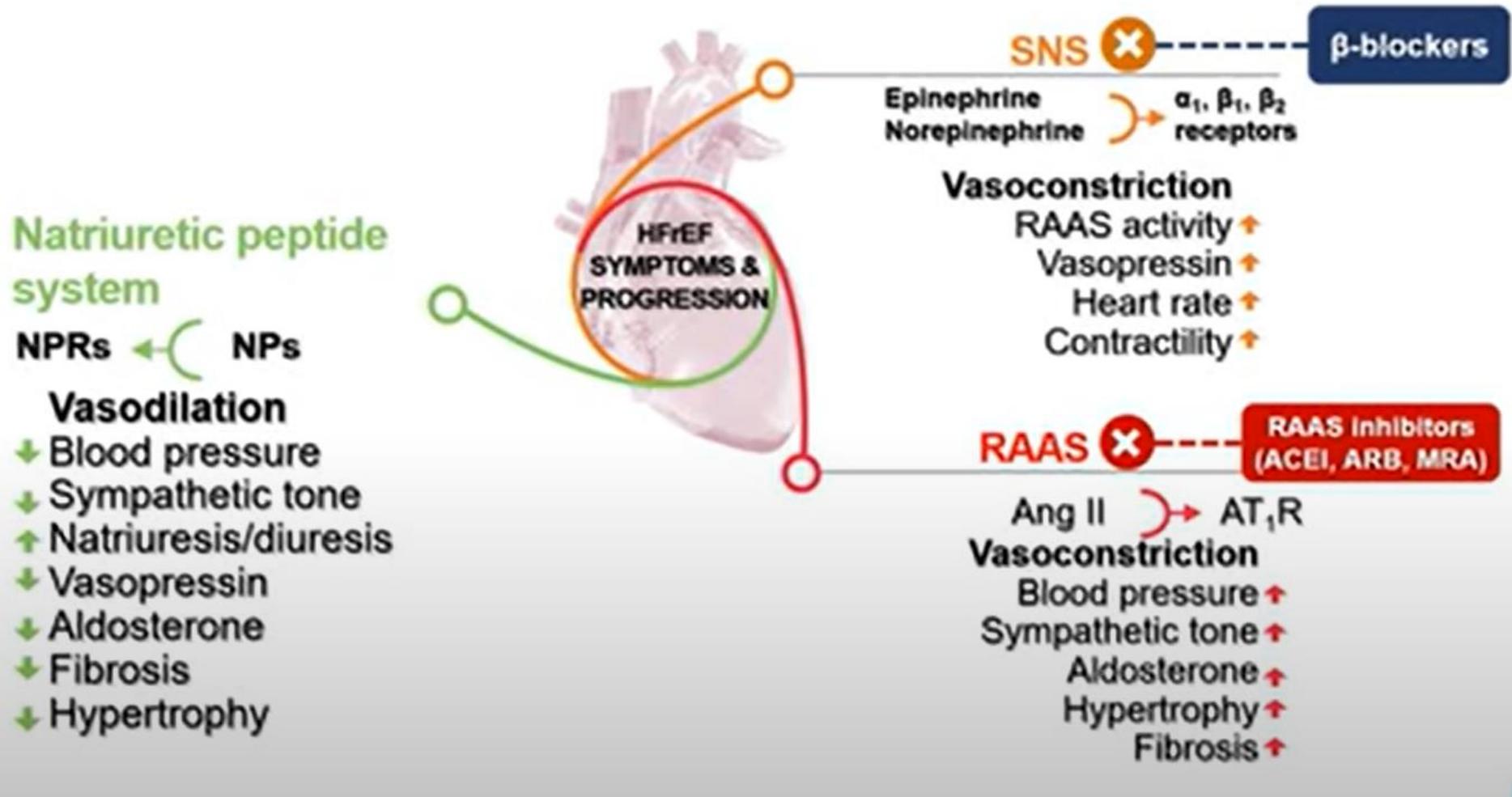
	Starting Dose	Target Dose
Beta blockers		
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	20-50 mg twice daily
Metoprolol XL	12.5-25 mg daily	200 mg daily
Ace Inhibitors		
Captoprilol	6.25 mg 3x daily	50 mg 3x daily
Enalapril	2.5 mg daily	20 mg twice daily
Lisinopril	5 mg daily	20-40 mg daily
Ramipril	1.25 mg daily	10 mg daily

	Starting Dose	Target Dose
ARB		
Candesartan	4-8 mg daily	32 mg daily
Losartan	50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
MRA		
Eplerenone	25 mg daily	50 mg daily
Spirinolactone	12.5-25 mg daily	25-50 mg daily
Vasodilators		
Hydralazine	25 mg 3x daily	75 mg 3x daily
Isorobide dinitrate	20 mg 3x daily	40 mg 3x daily

New(ish) Therapies

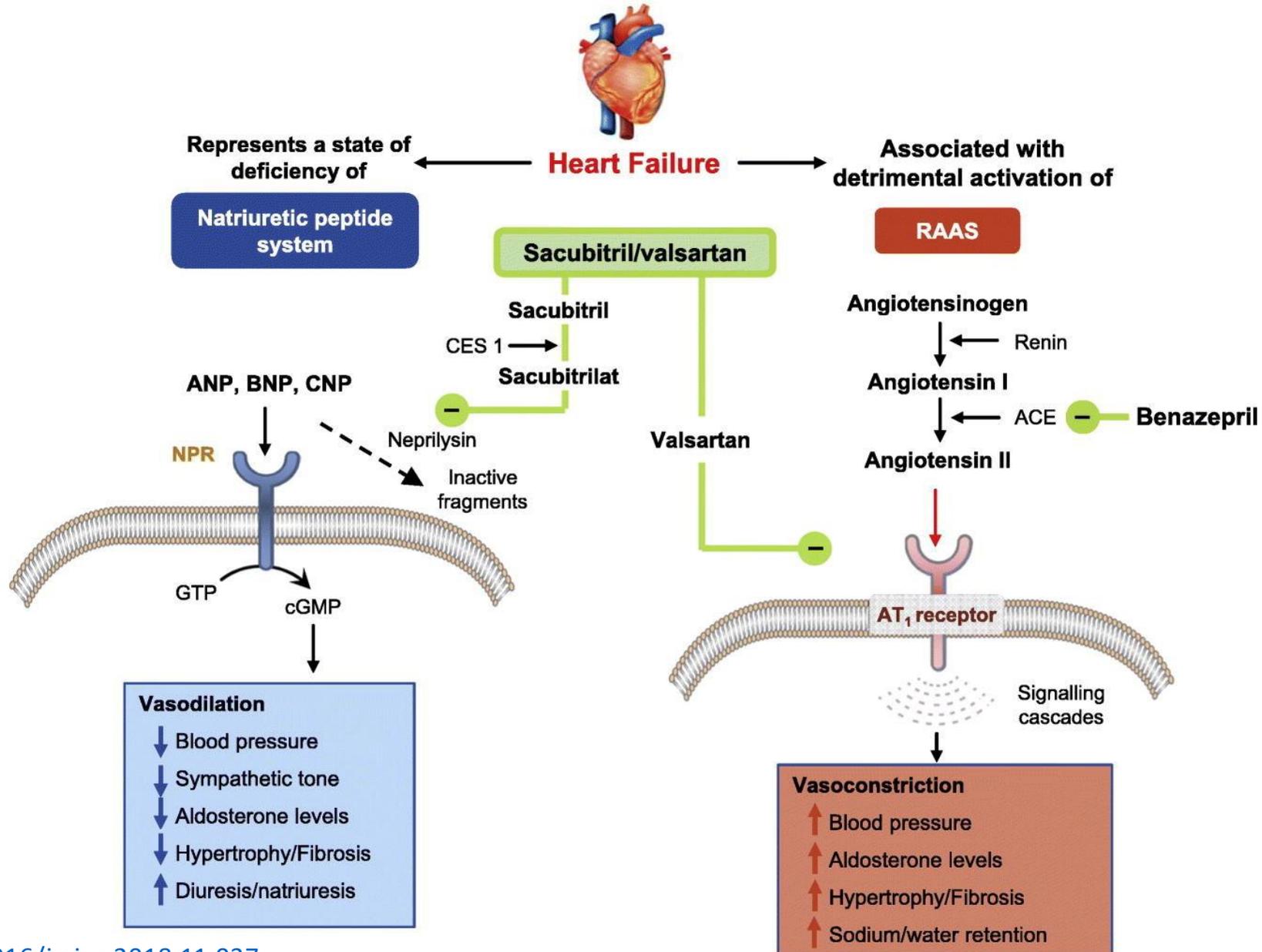
- ARNI Therapy
- SGLT2 inhibitors





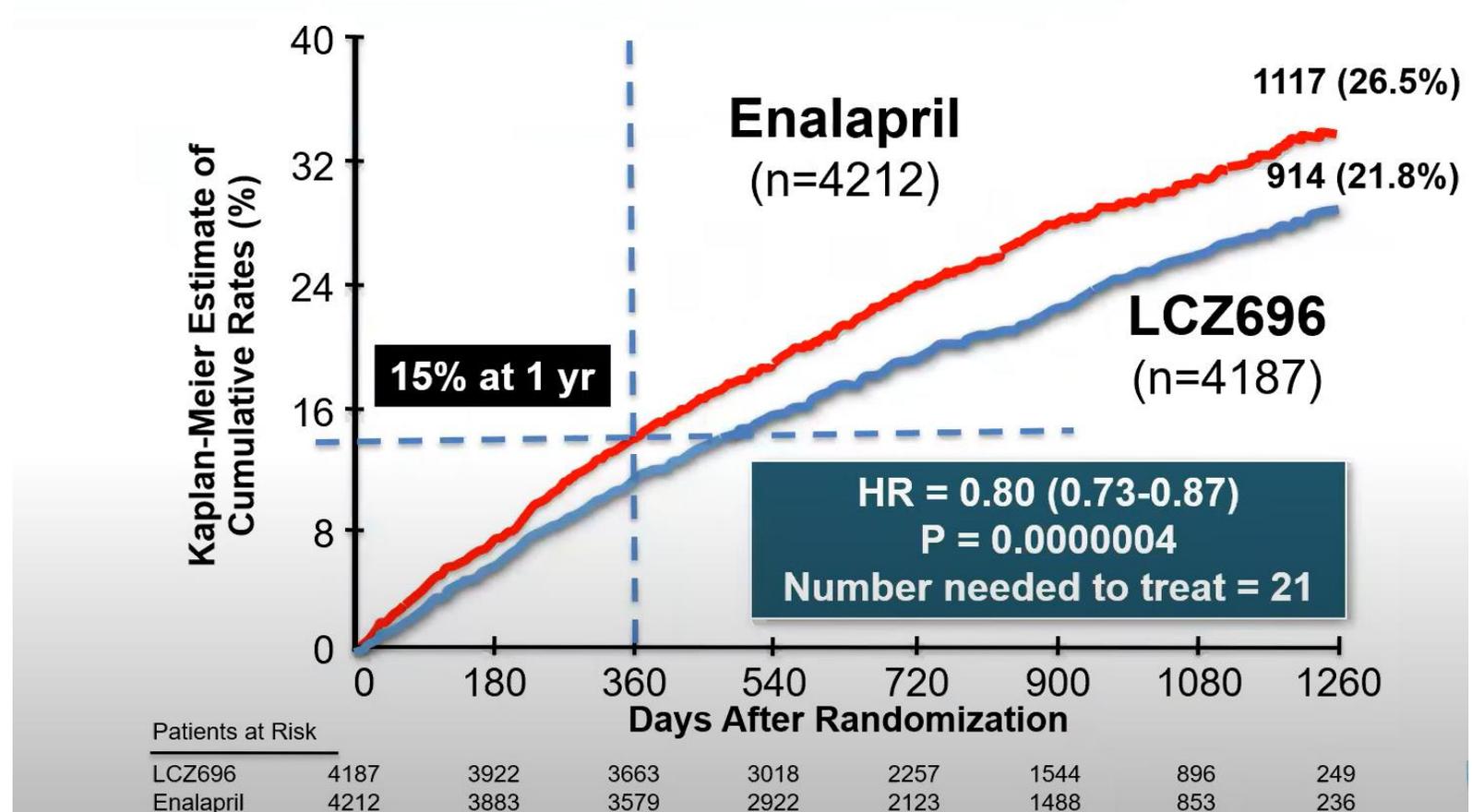
ARNI Therapy

Mechanism of action of ARNI therapy



Paradigm-HF

- Randomized, blinded, parallel trial in which 8,442 patients with HFrEF (EF <40%) were randomized to ARNI vs Enalapril
- Primary endpoints included cardiovascular death or hospitalization from heart failure



PROVE-HF

Table 3. Change in Cardiac Remodeling Measurements From Baseline to 6 and 12 Months After Initiation of Sacubitril-Valsartan Among Patients With New-Onset HF or Not Taking ACEI or ARB at Baseline

New-Onset HF or ACEI/ARB Naive	Baseline Value, Median (25th to 75th Percentile)	6-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 6 mo (95% CI)	P Value	12-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 12 mo (95% CI)	P Value
LVEF, %	n = 108	n = 102			n = 98		
Yes	28.4 (25.2 to 33.9)	35.7 (30.7 to 42.1)	6.9 (5.7 to 8.0)	<.001	43.5 (35.4 to 50.5)	12.8 (11.05 to 14.5)	<.001
No	28.1 (24.3 to 32.6)	33.8 (28.7 to 39.1)	4.9 (4.5 to 5.3)	<.001	37.0 (31.8 to 44.4)	8.8 (8.3 to 9.3)	<.001
LVEDVI, No., mL/m ²	n = 108	n = 102			n = 98		
Yes	85.97 (70.13 to 95.47)	74.59 (62.70 to 85.90)	-7.21 (-8.50 to -5.93)	<.001	67.66 (57.77 to 79.39)	-13.81 (-15.78 to -11.83)	<.001
No	87.43 (76.89 to 101.38)	80.38 (70.46 to 93.89)	-6.56 (-7.05 to -6.07)	<.001	75.12 (64.11 to 86.83)	-12.00 (-12.71 to -11.29)	<.001
LVESVI, No., mL/m ²	n = 108	n = 102			n = 98		
Yes	59.28 (48.64 to 71.29)	46.29 (36.44 to 58.94)	-10.01 (-11.45 to -8.58)	<.001	37.69 (28.97 to 51.16)	-17.88 (-20.07 to -15.68)	<.001
No	61.82 (52.70 to 75.91)	52.94 (43.28 to 66.42)	-8.46 (-9.01 to -7.90)	<.001	46.70 (36.47 to 58.1)	-14.86 (-15.64 to -14.09)	<.001
LAVI, No., mL/m ²	n = 101	n = 101			n = 98		
Yes	36.86 (31.53 to 45.02)	32.14 (25.24 to 38.78)	-4.83 (-5.84 to -3.83)	<.001	28.13 (23.32 to 35.53)	-8.44 (-9.73 to -7.15)	<.001
No	37.90 (31.63 to 46.25)	32.94 (27.90 to 40.65)	-4.28 (-4.68 to -3.88)	<.001	29.43 (25.04 to 35.90)	-7.42 (-7.85 to -6.99)	<.001
E/e', No.	n = 84	n = 88			n = 89		
Yes	11.85 (8.35 to 16.60)	9.70 (7.00 to 14.25)	-1.86 (-3.01 to -0.70)	.002	9.00 (6.80 to 12.70)	-2.60 (-3.83 to -1.37)	<.001
No	11.60 (8.80 to 16.00)	10.60 (7.80 to 14.80)	-1.13 (-1.56 to -0.70)	<.001	10.30 (7.80 to 14.40)	-1.10 (-1.57 to -0.63)	<.001

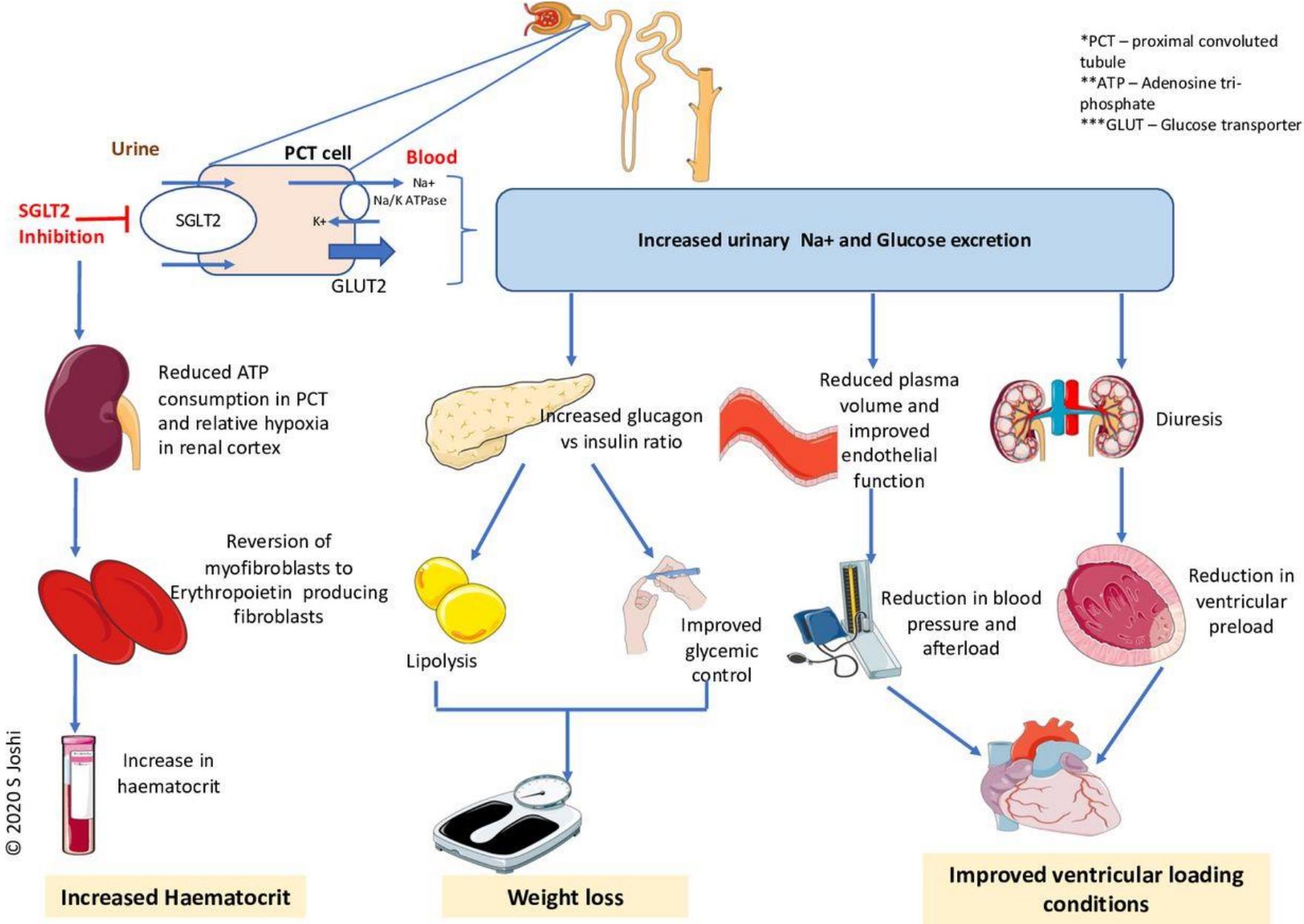
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; E/e', ratio of early transmitral Doppler velocity/early diastolic annular velocity; HF, heart failure; LAVI, left atrial volume

index; LS, least-square; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; No, not in the subgroup; Yes, in the subgroup.

- Exploratory, open label study in patients with HFrEF (EF <40%) published subsequently after Paradigm-HF
- 794 patients included that were started on or switched to ARNI therapy
- Primary endpoint was changes in NT-proBNP and correlation with cardiac reverse remodeling

SGLT2 inhibitors

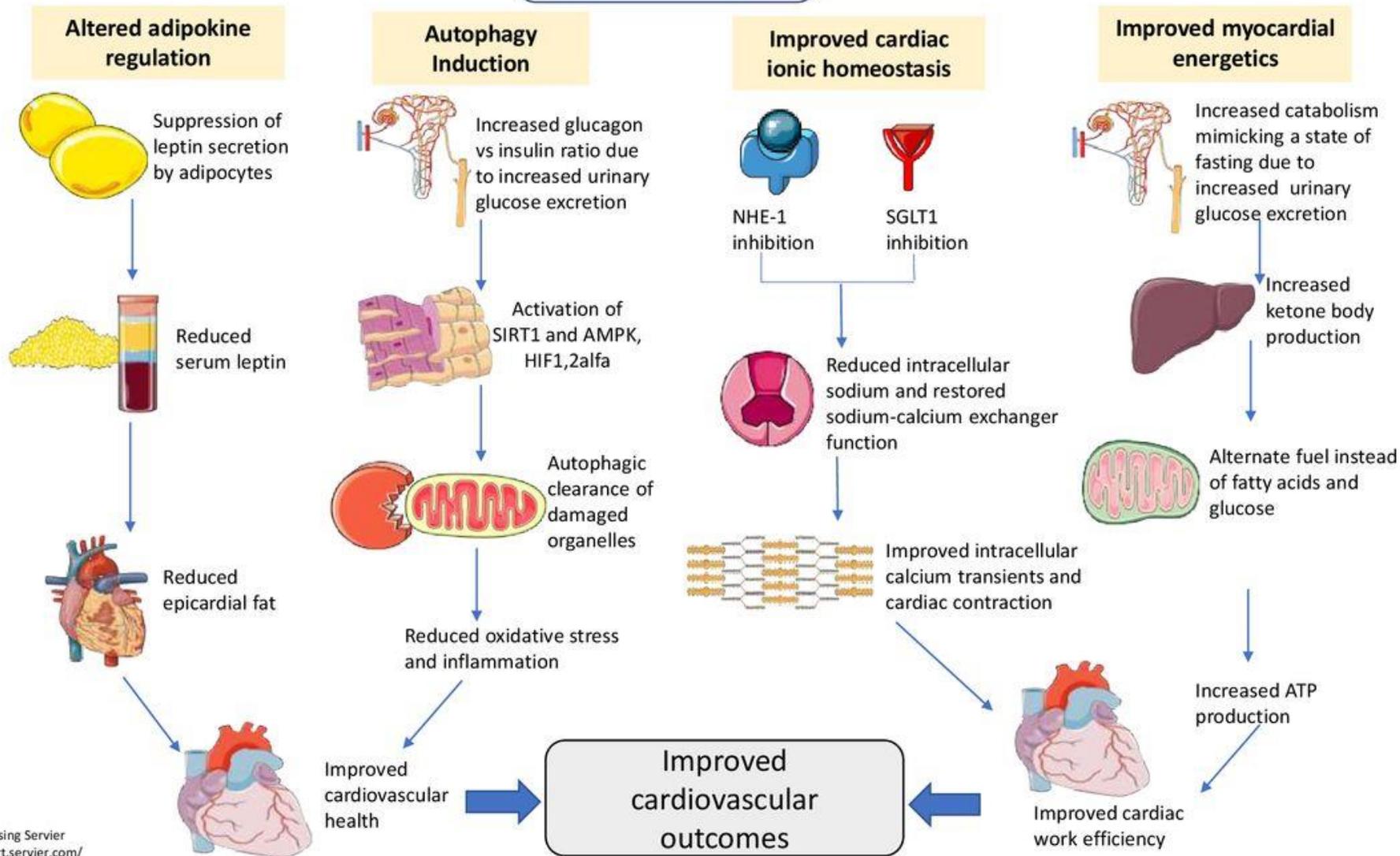
Mechanism of SGLT2 inhibitors



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Novel mechanisms of benefit in heart failure with SGLT2 inhibition



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SGLT2 inhibitors in heart failure

ORIGINAL ARTICLE



Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Authors: John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., [+31](#), for the DAPA-HF Trial Committees and Investigators* [Author Info & Affiliations](#)

Published September 19, 2019 | N Engl J Med 2019;381:1995-2008 | DOI: 10.1056/NEJMoa1911303

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ORIGINAL ARTICLE



Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

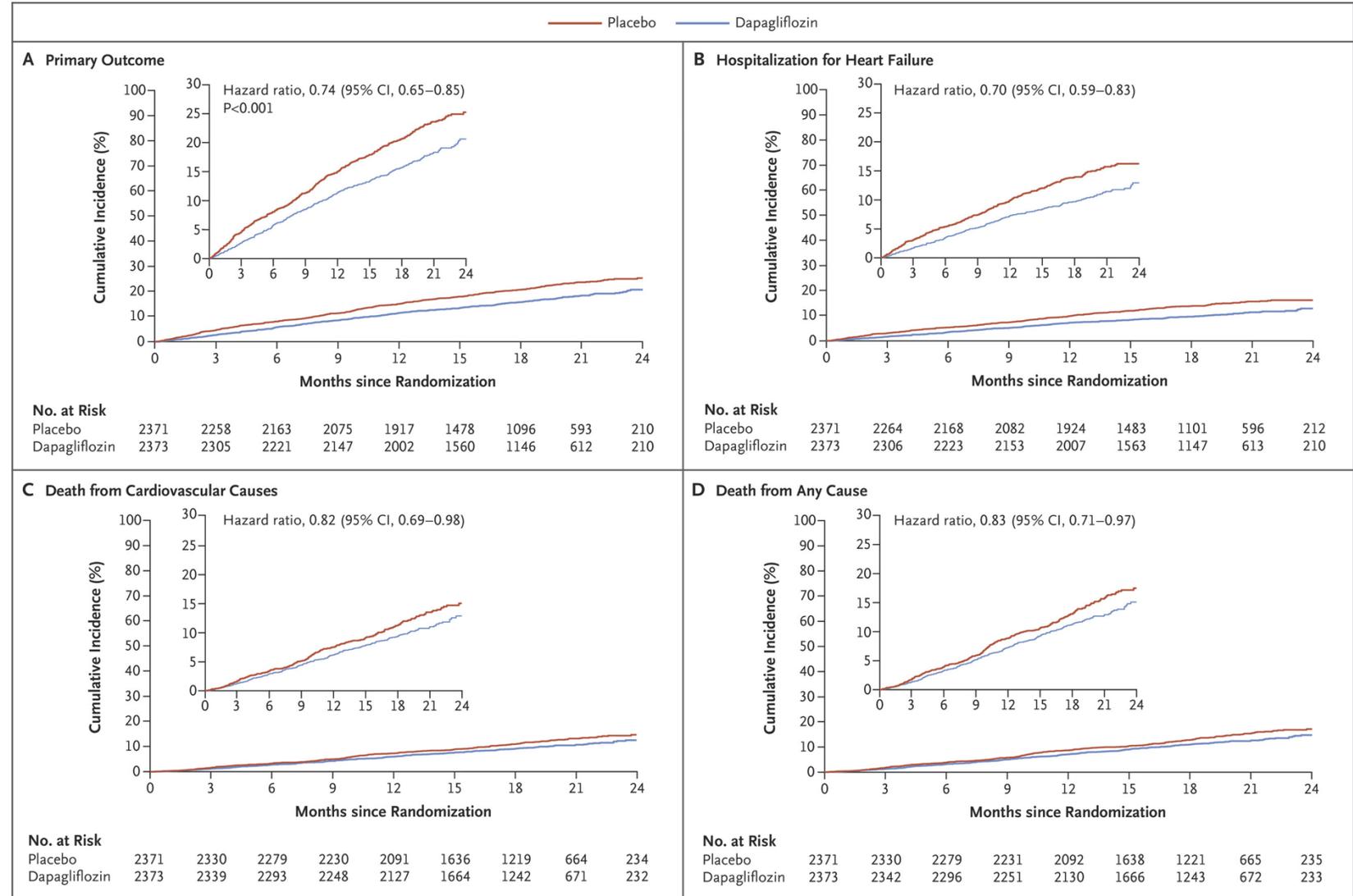
Authors: Milton Packer, M.D. , Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., [+32](#), for the EMPEROR-Reduced Trial Investigators* [Author Info & Affiliations](#)

Published August 28, 2020 | N Engl J Med 2020;383:1413-1424 | DOI: 10.1056/NEJMoa2022190

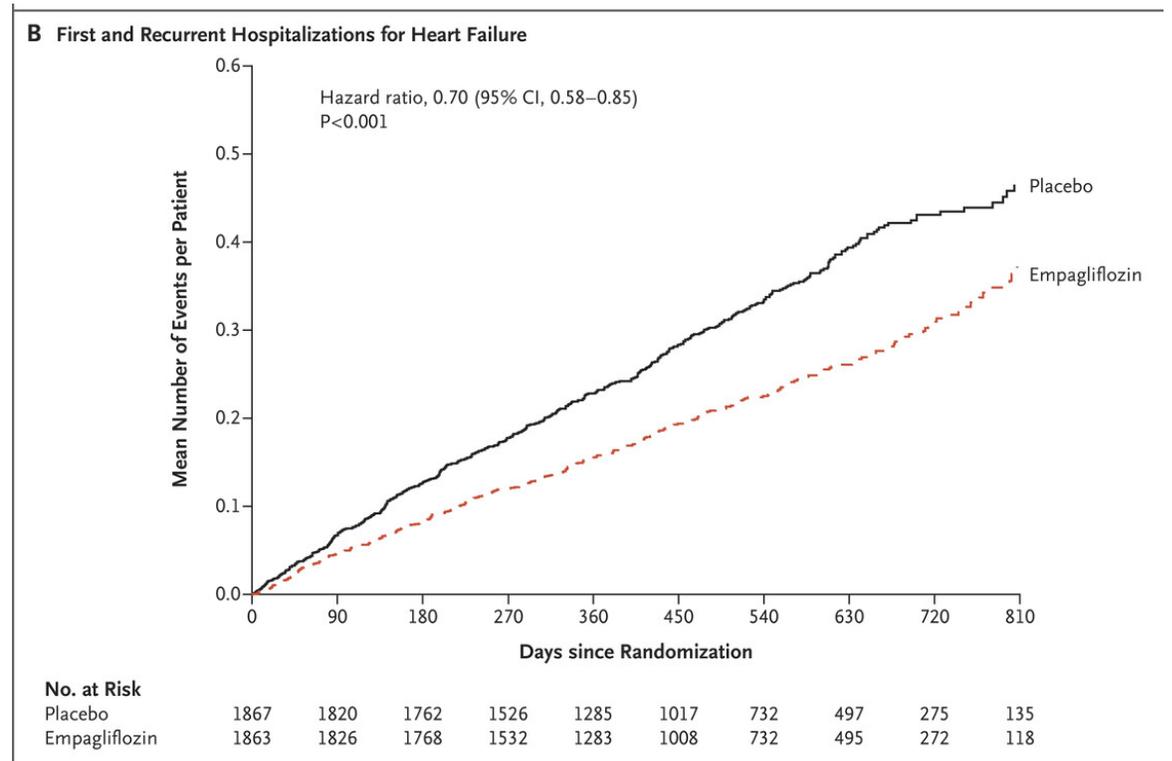
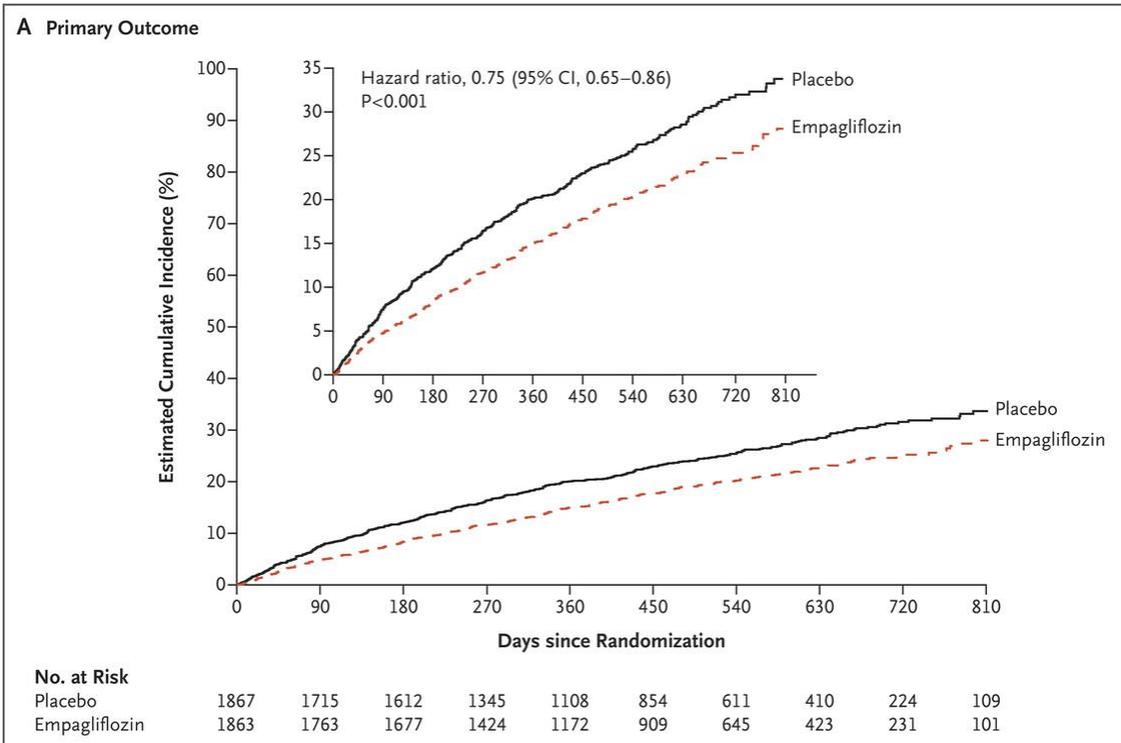
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DAPA-HF

- Randomized, parallel trial in which 4,744 patients with HFrEF (EF < 40%) were enrolled comparing dapagliflozin to placebo
- Patients enrolled irrespective of their diabetes status
- Primary outcome included cardiovascular death, hospitalization for heart failure, or urgent heart failure visit



Emperor- Reduced Trial



HFrEF benefit independent of glycemic status

Type 2 diabetes at baseline

Yes

215/1075

271/1064

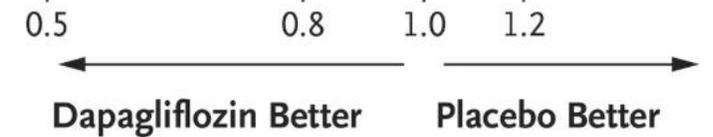
0.75 (0.63–0.90)

No

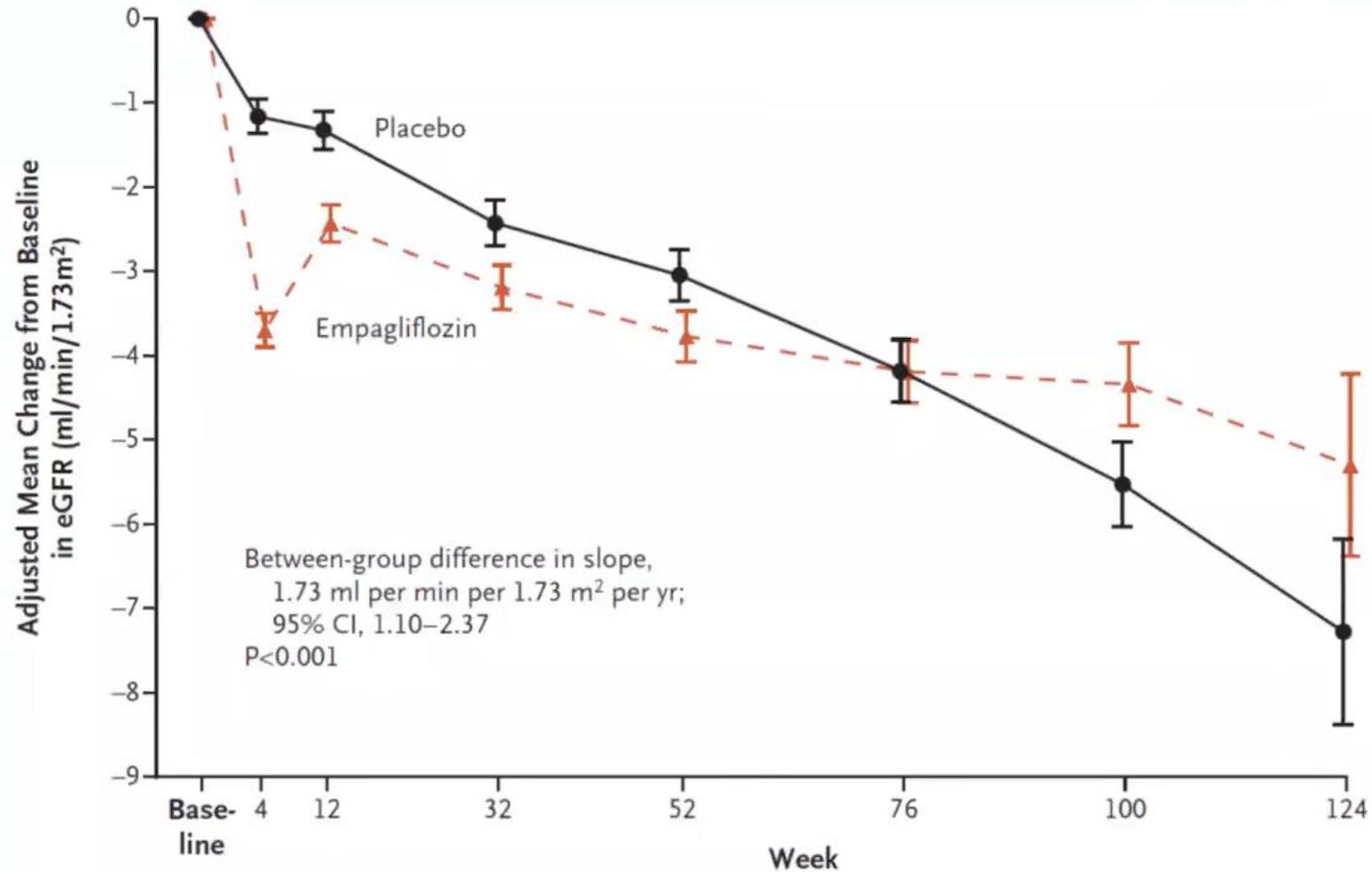
171/1298

231/1307

0.73 (0.60–0.88)



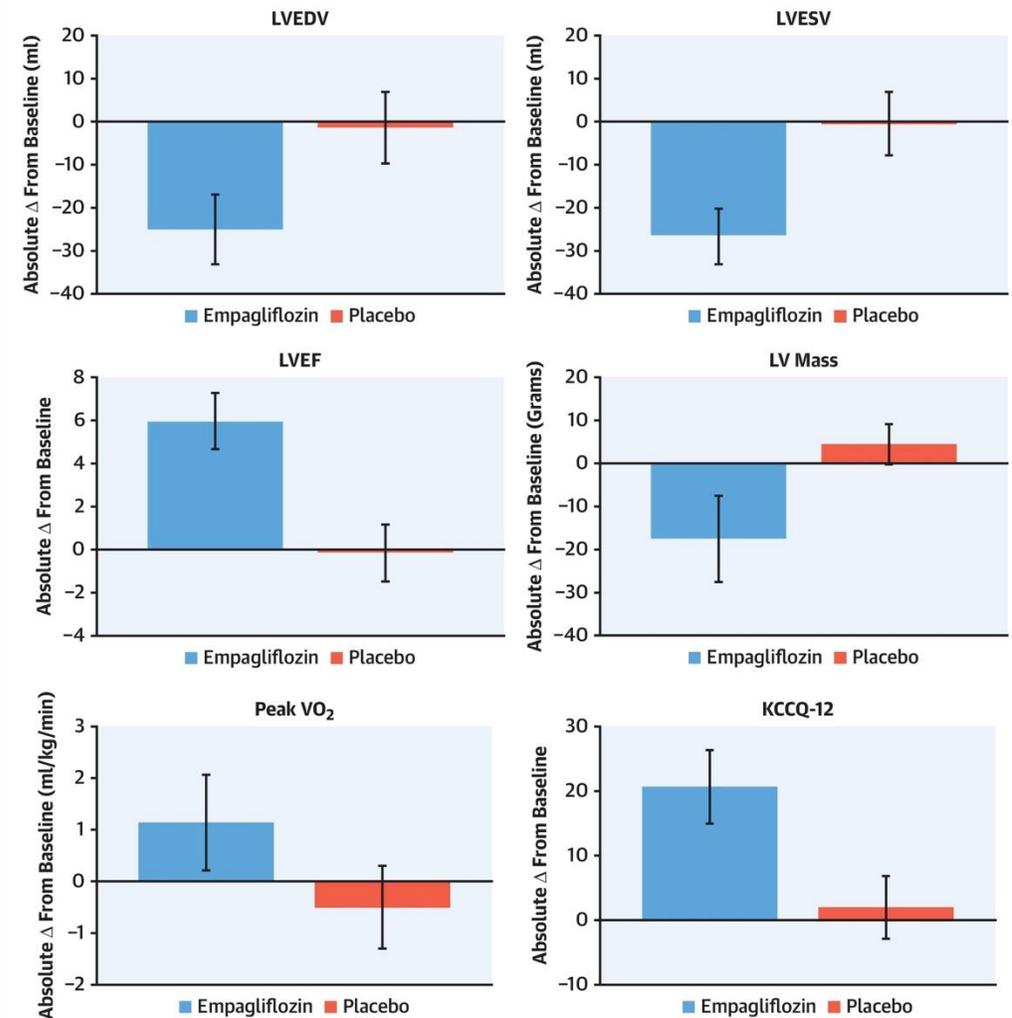
Emperor-Reduced: Renal endpoint



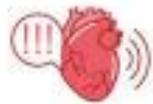
EMPATROPISM Study

- Study performed in 2021- single site, double blind, placebo controlled trial in which 84 patients were randomized to empagliflozin vs placebo for 6 months
- Study evaluated effects of Empagliflozin versus placebo in heart failure with reduced ejection fraction (LVEF <40%)
- Primary endpoint was change in LV end-diastolic and -systolic volume assessed by cardiac magnetic resonance. Secondary endpoints included changes in LV mass, LV ejection fraction, peak oxygen consumption in the cardiopulmonary exercise test, 6-min walk test, and quality of life.
- Statistically significant in all endpoints- LVEDV, LVESV, LVEF, LV Mass
- Larger impacts on remodeling and functional status (improvement in the peak VO₂) and Kansas City Cardiomyopathy Questionnaire

CENTRAL ILLUSTRATION: Empagliflozin in Nondiabetic Patients With Heart Failure With Reduced Ejection Fraction Improves Cardiac Function, Adverse Remodeling, and Exercise Capacity: A Randomized Control Trial



Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2021;77(3):243-55.

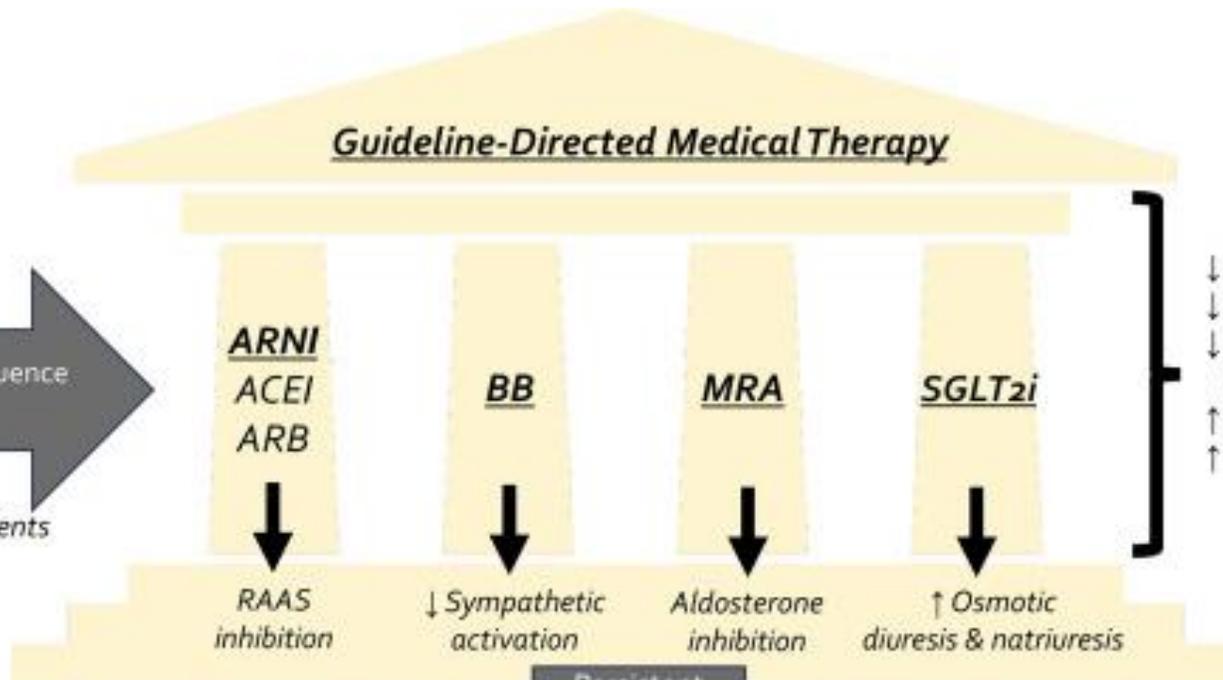


Heart Failure with
Reduced Ejection
Fraction (HFrEF)

Simultaneous or rapid sequence
initiation of GDMT



All patients



↓ Preload
↓ Afterload
↓ Myocardial O₂ demand
↑ Coronary perfusion
↑ Reverse cardiac remodeling



Diuretic therapy



Hydralazine-isosorbide dinitrate (1a)

Self-identified African-Americans,
NYHA Class III-IV



Ivabradine (2a)

NSR, resting HR ≥ 70 bpm

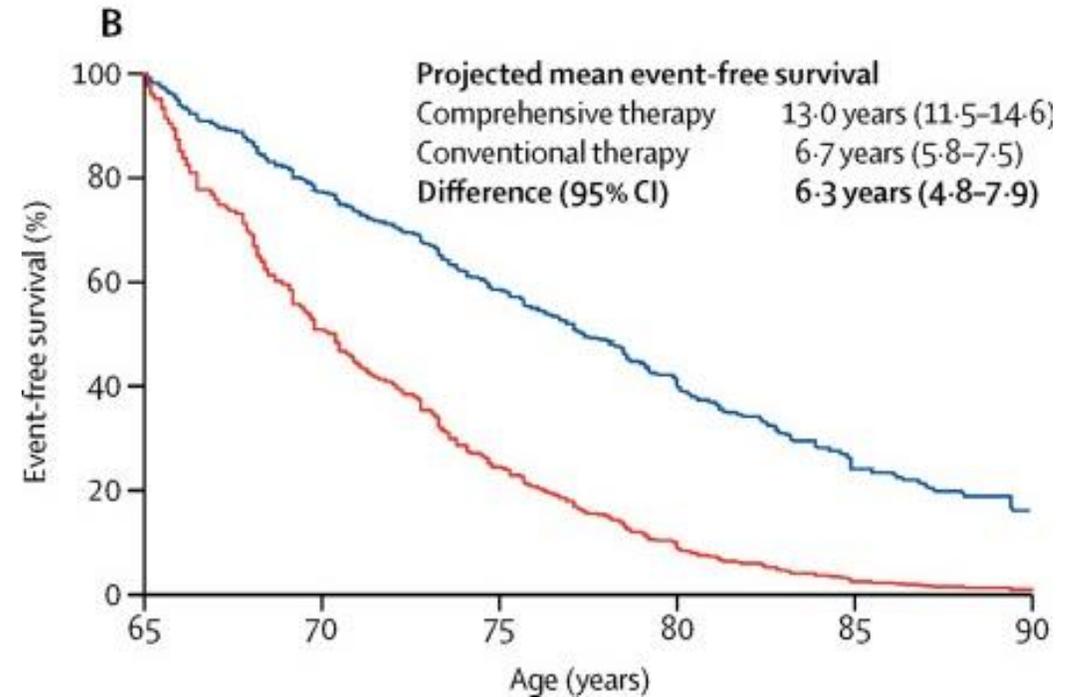
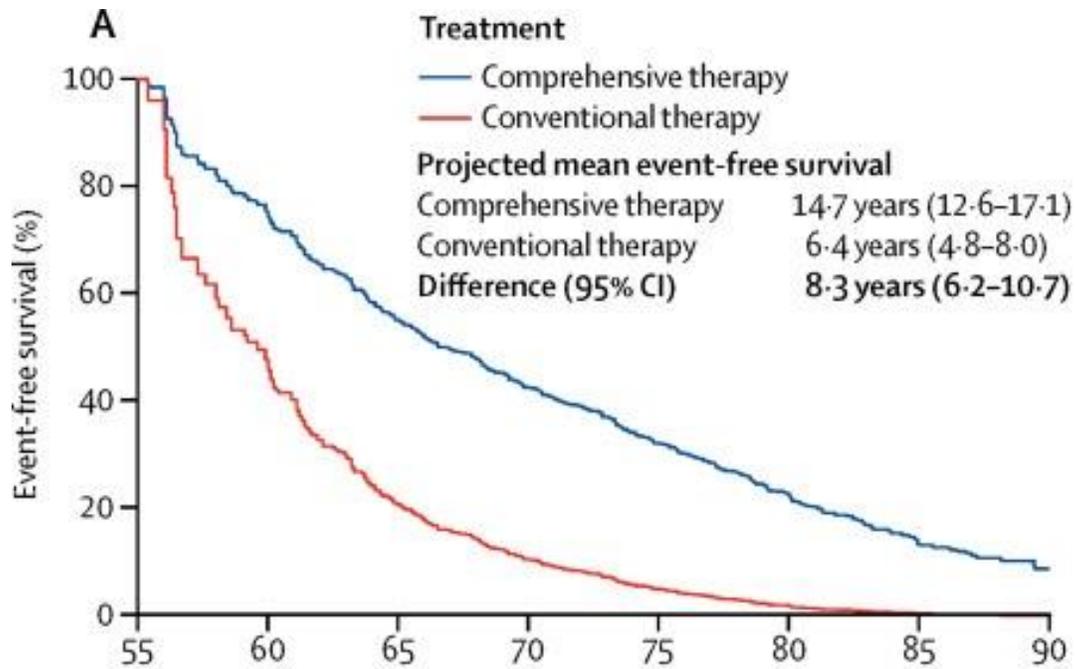


Soluble guanyl cyclase stimulator (Vericiguat) (2b)



Digoxin (2b)

Benefits of Quadruple Therapy



How do you initiate or escalate therapy?

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee  FREE ACCESS

Expert Consensus Decision Pathway

Thomas M. Maddox, James L. Januzzi, Larry A. Allen, Khadijah Breathett, Sara Brouse, Javed Butler, Leslie L. Davis, Gregg C. Fonarow, Nasrien E. Ibrahim, JoAnn Lindenfeld, Frederick A. Masoudi, Shweta R. Motiwala, Estefania Oliveros, Mary Norine Walsh, Alan Wasserman, Clyde W. Yancy, and Quentin R. Youmans **SEE FEWER AUTHORS** 

JACC. 2024 Apr, 83 (15) 1444–1488

“There is no optimal order of initiation and/or titration...clinicians will need to approach each patient in an individual fashion to decide which agents to titrate and when to do so”

“Careful initiation and titration of GDMT should be early and rapid as possible with a goal to use the 4 key medication classes in each patient...with goal of reaching target or maximally tolerated doses of the 4 key medication classes as soon as possible and ideally no longer than 3 months”

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

- Multinational randomized parallel-group trial of participants admitted with acute heart failure not on full doses of guideline directed medical therapy
- Demonstrated safety and efficacy of achieving 50% of target doses by hospital discharge and 100% of target doses by 2 weeks following discharge from hospital
- Patients achieving a higher percentage of optimal dose were associated with a reduced risk of death or being readmitted for heart failure at 180 days

What's Next?

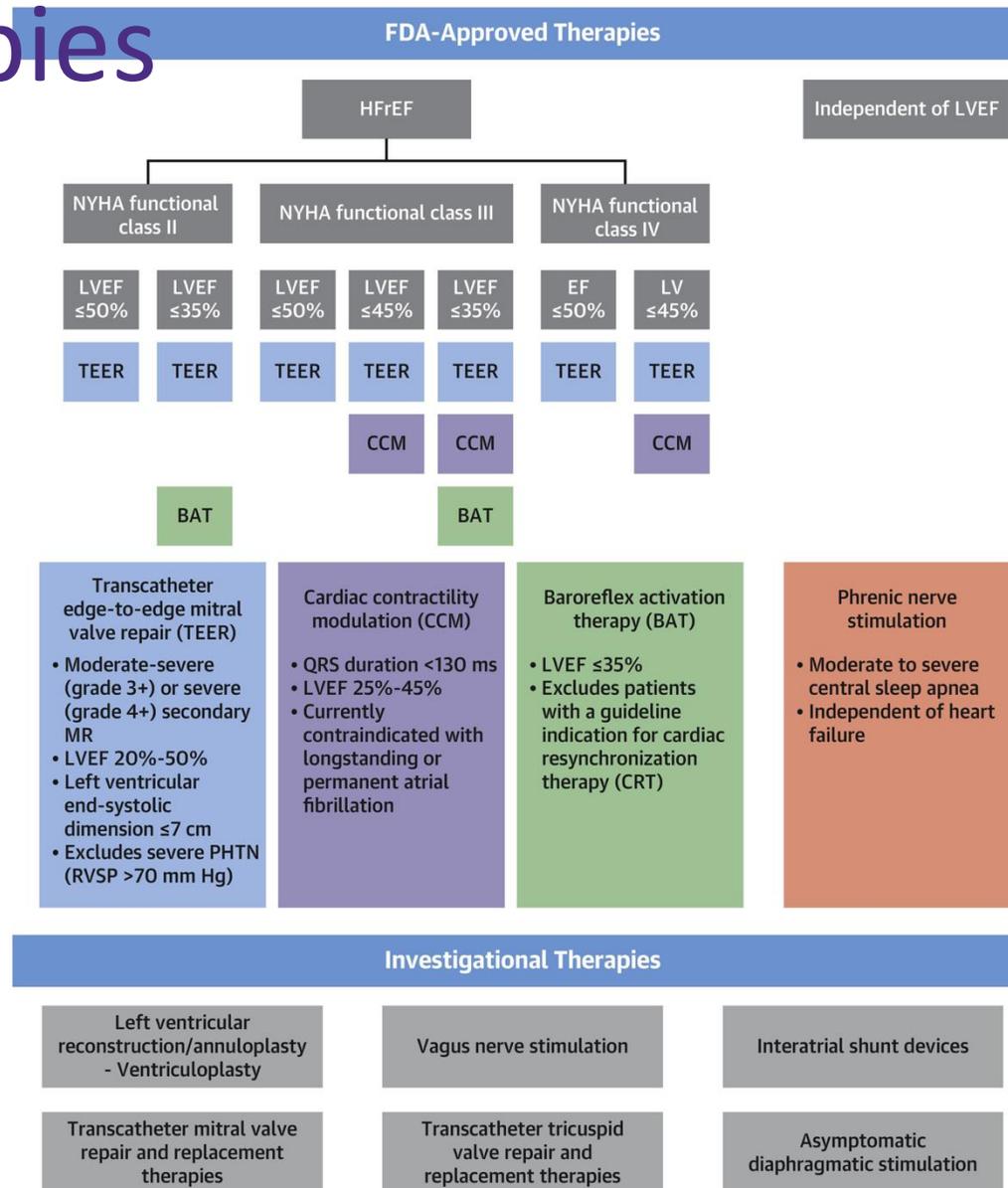
Medications on the horizon

- Vericiguat
 - Stimulated soluble guanylate cyclase
 - Stimulated sGC leading to improved myocardial function, improve left ventricular reverse remodeling, decrease fibrosis

- Omecamtiv mecarbil
 - Induced myosin to bind to actin and pull on the actin filaments
 - “Oral inotrope”
 - Mechanism of actions lets to increases duration of systole, stroke volume without changing or increasing myocardial oxygen consumption

Device Therapies

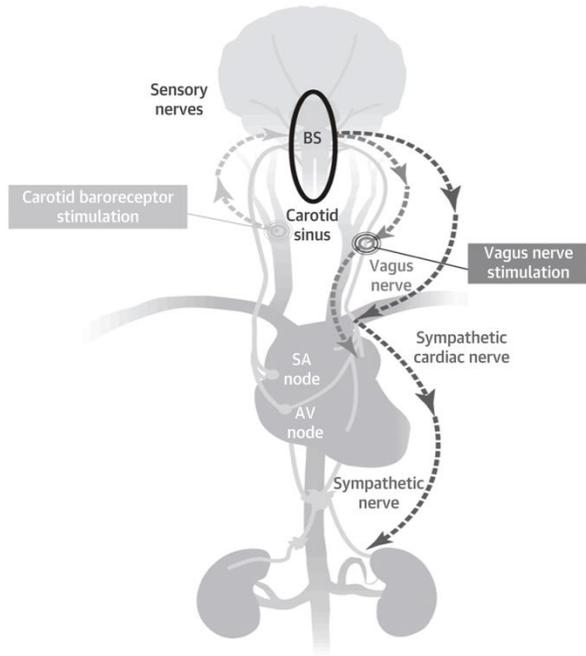
CENTRAL ILLUSTRATION: U.S. Food and Drug Administration-Approved and Breakthrough Designated Device Therapies



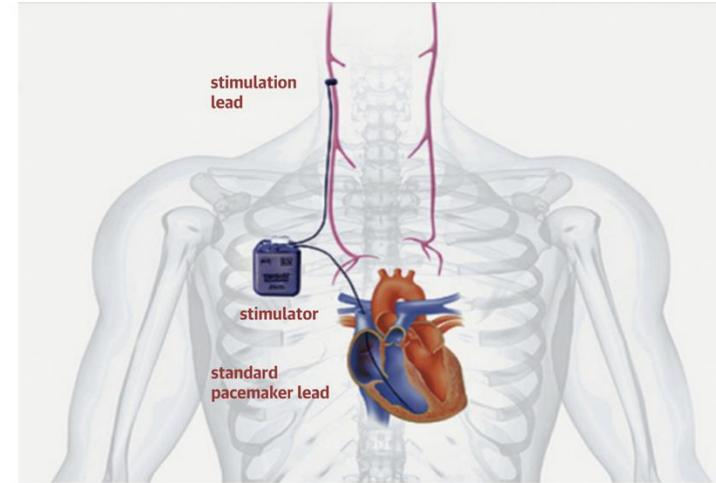
Autonomic modulation

- Excessive activation of the sympathetic nervous system with decreased parasympathetic nervous system activity occur as adaptive mechanisms to cardiac injury, congestion, and decreased stroke volume
- Long-term sympathetic nervous system stimulation and parasympathetic nervous system depression accelerate cardiovascular stress and ventricular remodeling
- Stimulation of the vagus nerve has been introduced in an attempt to counter these long-term deleterious effects

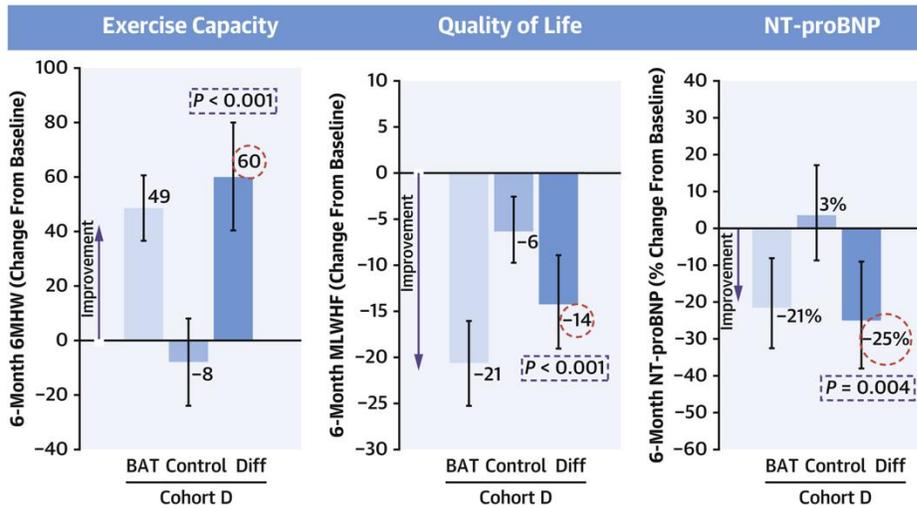
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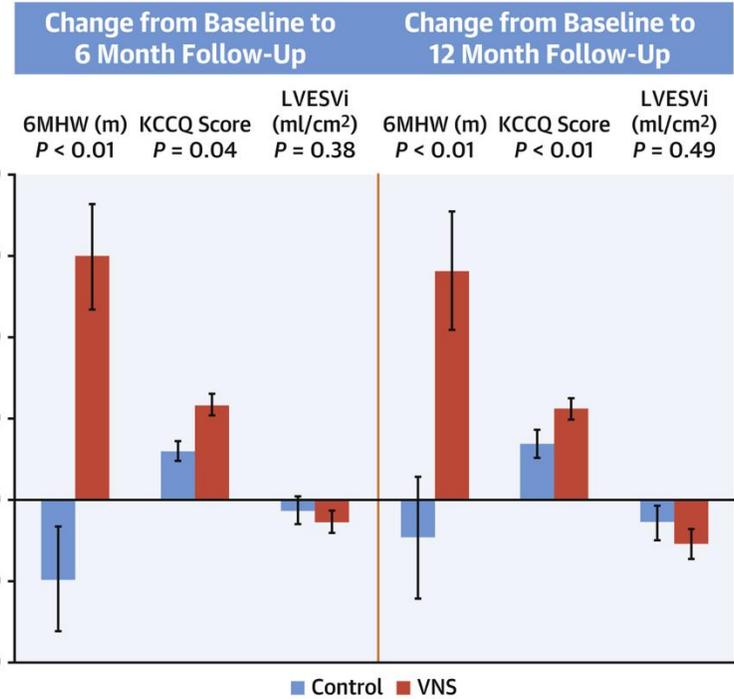
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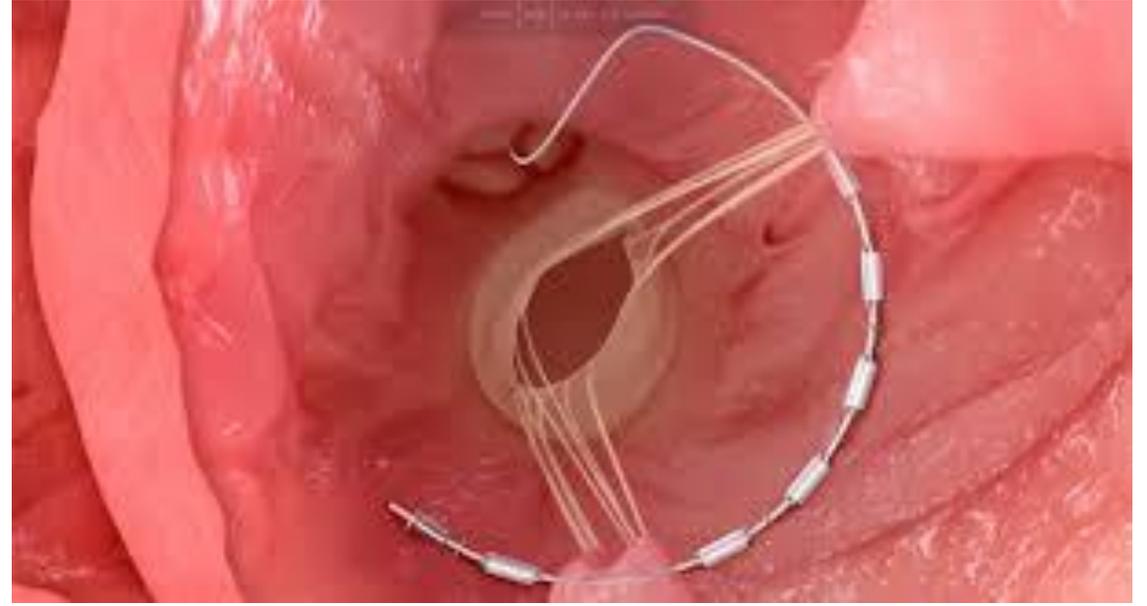


D



Left ventricular reconstruction

- Ischemic cardiomyopathy and LV remodeling are characterized by expansion and thinning of the LV wall and loss of the typical LV elliptical shape, leading to an increase in the wall tension and inefficient ventricular contraction
- Left ventricular reconstruction has been considered as a potential treatment for selected patients with HF



THE CORCINCH-HF STUDY

An evaluation of the Ventricular Restoration System in symptomatic heart failure patients with reduced ejection fraction (HFrEF)

In Summary

- The University Definition of Heart failure is defined by classification of EF, clinical and laboratory data, and stages
- However, it should be recognized that heart failure presentation is on a spectrum, and severity of heart failure is not always correlated by the EF
- Regardless of the ejection fraction, there are similar mechanisms in the pathophysiology and manifestation of heart failure, and mortality is high if undiagnosed or undertreated
- In the treatment of heart failure with reduced ejection fraction, the early initiation of medical therapy with inclusion and uptitration of all 4 pillars of medical therapy is paramount to event-free survival

Case Presentation

He is started on IV diuretics and transitioned to oral diuretics. He is discharged on the following medications:

- Losartan 25 mg daily
- Spironolactone 12.5 mg daily
- Metoprolol succinate 25 mg daily
- Furosemide 40 mg daily

He is now following up with in the office one week after discharge. What would be the next best step in his management?

- A) Attempt to further optimize his medical therapy
- B) Refer for primary prevention implantable cardioverter-defibrillator
- C) Refer for transplant/LVAD evaluation
- D) Nothing- monitor his progress and his symptoms

Questions?

