How to Manage Advanced Heart Failure Patients

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1

Disclosure

Consultant: Boehringer-Ingelheim

Speaker's Bureau: Boehringer-Ingelheim

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Objectives

- To understand the nomenclature associated with heart failure categories
- Implement the latest recommended heart failure treatments to patients under their care
- After hearing the presentation, the participant should be able to apply referral guidelines for Advanced Heart Cardiology to their practice

3

US Heart Failure (HF) Statistics

- **6.5 million** Adults in the US have heart failure
- HF was a contributing cause of **1 in 8 deaths** in 2017
- Approximately **HALF** of people who develop HF **Die** w/i **5 yrs of initial diagnosis**
- **NYHA Class IV** patients have an annual **Mortality rate of > 50%**
- **HF Goal Directed Medical Therapy (GDMT) only Reduces Mortality in HFrEF**
- **Highest Mortality Rates in African American Men**

Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–528.
Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2017. Accessed January 7, 2019.

4

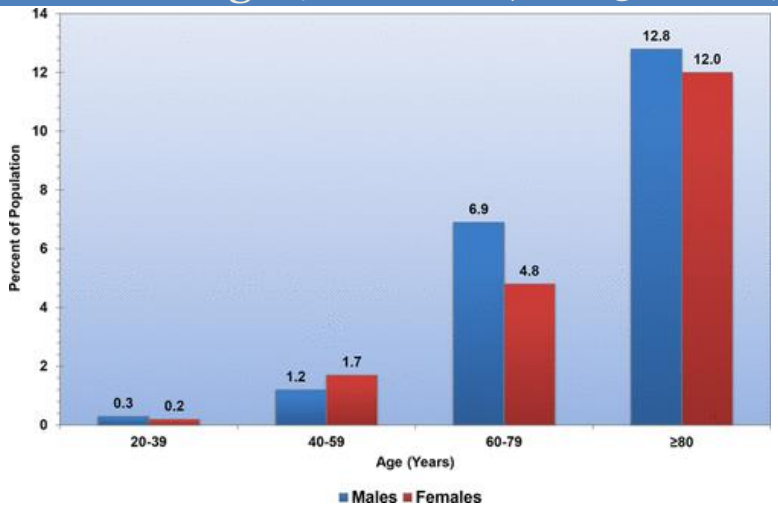
US Heart Failure Statistics

- **US adults 65 years and older increased 22.9% from 41.4 million to 50.9 million between 1/1/2011 – 12/31/2017**
  - Population of adults younger than 65 years increased by only 1.7%
- **Age-adjusted Mortality rates**
  - Decreased 5.0% for Heart Disease (HD)
  - Decreased 14.9% for Coronary Heart Disease (CHD) while increasing
  - **INCREASED 20.7% for HEART FAILURE**
- **The number of Heart Failure Deaths INCREASED by 38 %**
  - **A total of 80% of HD deaths occurred in the group of adults aged 65 years and older**

Sidney S, Go A, Jaffe M, Solomon M, Ambrosy A, Rana J. Association between aging of the US population and heart disease mortality from 2011 to 2017. JAMA Cardiol. 2019 Oct 30. doi: 10.1001/jamacardio.2019.4187. [Epub ahead of print]

5

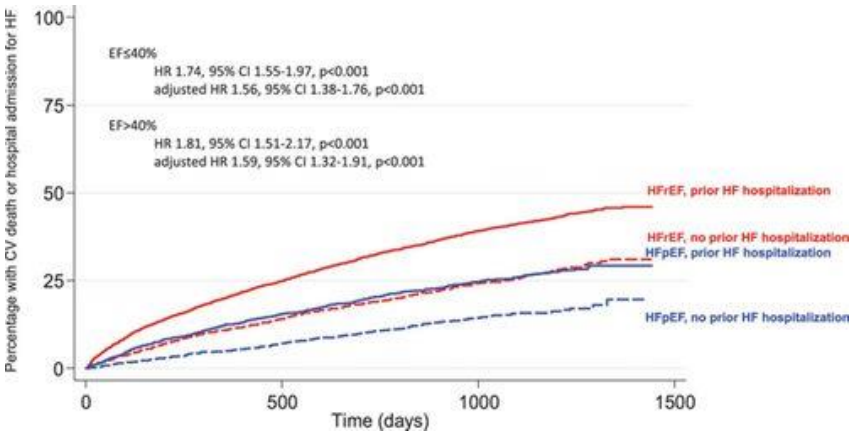
Prevalence of Heart Failure for Adults ≥ 20 Years by Sex and Age (NHANES, 2013–2016)



Emelia J. Benjamin. Circulation. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association, Volume: 139, Issue: 10, Pages: e56-e528, DOI: (10.1161/CIR.0000000000000659)

6

Previous Hospitalization HF (HHF) Is Associated with Increased Risk of CV Death & HFF Independent of EF (CHARM Registry)



Bello NA, Claggett B, Desai AS, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Solomon SD. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction.Circ Heart Fail. 2014; 7:590–595. doi: 10.1161/CIRCHEARTFAILURE.113.001281

7

Case 1

Mr. AB is a 32-year-old self-identified African American man with no significant past medical history Is seen in your office for follow up of abnormal cardiac testing. The patient had a yearly physical performed the week prior and had asymptomatic sinus tachycardia at rest. An EKG demonstrated sinus tachycardia 120 bpm. He works as an attorney but denies any recent stressors since switching from civil to corporate law. He plays tennis twice a week, and exercises at a high-end gym for 45 mins 3 times a week without any episodes of shortness of breath. He denies any palpitations, orthopnea, dyspnea on exertion, or syncope.

He was sent for an echocardiogram which revealed a mildly dilated left ventricle, left ventricular ejection fraction 38%, mild mitral valve regurgitation, and no other significant abnormalities. His lab work was grossly unremarkable except for and elevated BNP level of 500 pg/mL. The patient has an older brother that died a few years ago in his sleep. He has three younger siblings, a wife, and two young children.

Which of the Following Statements Are True?

A. The patient has a diagnosis of heart failure as evidenced by his low ejection fraction, and elevated biomarker (BNP)

B. The patient's condition does not meet the technical definition for heart failure since he is asymptomatic

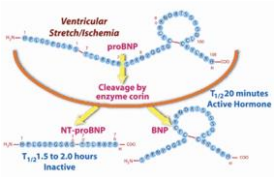
C. The patient's resting sinus tachycardia is a result of stress from racial discrimination

D. The patient has heart failure with preserved ejection fraction since he remains asymptomatic

Heart Failure Definition

Heart Failure (HF) is a clinical syndrome with current or prior

- Symptoms and/or signs caused by a **structural and/or functional** cardiac abnormality such as:
  - LVEF < 50%
  - Enlarged Left Ventricular Chamber size
  - Diastolic Dysfunction
  - Ventricular Hypertrophy
  - Moderate or severe valvular abnormality



- **AND** corroborated by at least one of the following:
  - **Elevated brain natriuretic peptide (BNP) levels**
  - BNP is released by ventricular cardiomyocytes in response to ↑ LV pressures
    - Ambulatory Patients: BNP > 35. NT-proBNP > 125 pg/mL
    - Hospitalized Patients: BNP > 100, NT-proBNP >300 pg/mL
  - Objective evidence of cardiogenic, pulmonary, or systemic **congestion** by diagnostic modalities or hemodynamic measurement at rest or with provocation

Bozkurt B, Coats AJ, Tsutsui H, et al. 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 [published online ahead of print, 2021 Mar 1]. *J Card Fail*. 2021;S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022

What Are the Next Best Steps?

A. Perform genetic testing, no need to start medical therapy for heart failure since he is asymptomatic
B. Perform genetic testing, investigate for reversible causes of heart failure, and start the patient on an evidenced-based beta-blocker and angiotensin converting enzyme inhibitor (ACEI)
C. Start the patient on any beta-blocker and angiotensin receptor blocker
D. Repeat labs and echocardiogram in a few months

11

Genetic Cardiomyopathy

Table 7. Examples of Factors Implicating Possible Genetic Cardiomyopathy

Phenotypic Category	Patient or Family Member Phenotypic Finding*	Ask Specifically About Family Members* With
Cardiac morphology	Marked LV hypertrophy	Any mention of cardiomyopathy, enlarged or weak heart, HF. Document even if attributed to other causes, such as alcohol or peripartum cardiomyopathy
	LV noncompaction	
	Right ventricular thinning or fatty replacement on imaging or biopsy	
Findings on 12-lead ECG	Abnormal high or low voltage or conduction, and repolarization, altered RV forces	Long QT or Brugada syndrome
Dysrhythmias	Frequent NSVT or very frequent PVCs Sustained ventricular tachycardia or fibrillation	ICD Recurrent syncope Sudden death attributed to "massive heart attack" without known CAD Unexplained fatal event such as drowning or single-vehicle crash
	Early onset AF	"Lone" AF before age 65 y
	Early onset conduction disease	Pacemaker before age 65 y
Extracardiac features	Skeletal myopathy Neuropathy Cutaneous stigmata Other possible manifestations of systemic syndromes	Any known skeletal muscle disease, including mention of Duchenne and Becker's, Emory-Dreifuss limb-girdle dystrophy Systemic syndromes: Dysmorphic features Mental retardation Congenital deafness Neurofibromatosis Renal failure with neuropathy

Heidenreich et al Circ 2022

12

Testing for Genetic Cardiomyopathies

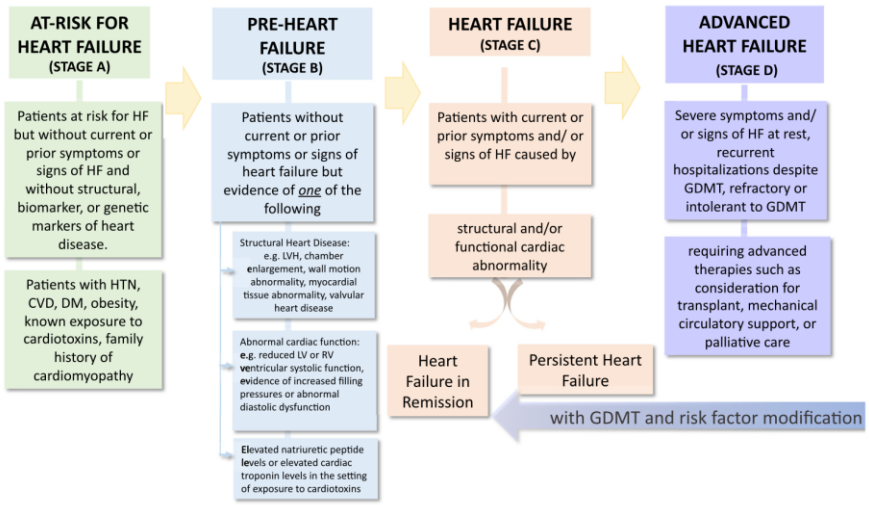
Recommendations for Genetic Evaluation and Testing
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	1. In first-degree relatives of selected patients with genetic or inherited cardiomyopathies, genetic screening and counseling are recommended to detect cardiac disease and prompt consideration of treatments to decrease HF progression and sudden death.[1,2]
2a	B-NR	2. In select patients with nonischemic cardiomyopathy, referral for genetic counseling and testing is reasonable to identify conditions that could guide treatment for patients and family members.[3,4]

Heidenreich et al Circ 2022

13

Stages Of Heart Failure



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14

HFrEF Treatment – Stage B

- Aggressive risk factor modification
- Medical therapy
  - **ACEI (or ARB) & Evidenced based Beta Blockers**
  - No role for digoxin or aldosterone antagonists
- ICD in selected patients
- Coronary revascularization if evidence of ischemia and viable myocardium
- Valve replacement or repair in selected patients

15

Case 2

Mr. AB is now 36 y/o man who was diagnosed with heart failure with reduced ejection fraction (HFrEF) 4 years ago and experienced improvement in his left ventricular ejection fraction to 48% with medical therapy. He presents to the hospital feeling shortness of breath with exertion for 2 weeks. He reports compliance with all his home medications but states his pants have been tightening around the waste and he becomes SOB tying his shoes. He is not sure how many pillows he sleeps with because he sleeps on an inclined mattress. However, he does endorse waking up SOB at night, and sitting at the edge of the bed to catch his breath for the last week. His medical regimen includes Lisinopril 20 mg daily, and Carvedilol 12.5 mg daily.

In the emergency department his blood pressure is 145/82 mmHg, HR 72 bpm, and respiratory rate is 18-22 bpm saturating 92% on room air. On physical exam his JVP was elevated to the angle of the jaw on end-expiration at a 45-degree angle. He had bilateral rales in his lungs, and a third heart sound. His extremities were warm with strong distal pulses, and no edema was present. His chest Xray has evidence of pulmonary edema. Pertinent labs reveal a mildly elevated creatinine, normal sodium, normal potassium, normal lactic acid levels, and an elevated BNP level of 5000 pg/mL.

What Is the Likely Diagnosis?

A. Cardiogenic Shock
B. COPD Exacerbation
C. Acute on chronic stage C heart failure (congestive heart failure)
D. Stage D Heart Failure

Heart Failure vs Cardiogenic Shock Signs & Symptoms

	History- Symptoms	Exam- Signs	Tests
Congestion (Fluid)	• Dyspnea On Exertion • Orthopnea • PND • Bendopnea • Cough • Abdominal distension • Weight gain • Edema	• Elevated JVP • 3rd Heart Sound • Lung Crackles • Ascites • Pulsatile Liver • Edema	• ↑Liver Enzymes • BNP or NTpBNP • Wet Lungs on CXR • Echocardiogram
Cardiogenic Shock	• Short of Breath at Rest • Fatigue • Nausea/Dry Heaving • Poor Appetite • Confusion • Weight Loss	• Low BP • Fast HR • Cool Extremities • Low Urination	• ↑Creatinine • ↑Liver Enzymes • Lactic Acid • Echocardiogram • Right Heart Catheterization

History & Physical Predictors of HF

	Sensitivity	Specificity	PPV	NPV	Odds Ratio
Rales > 1/3	15	89	69	38	1.4
JVP > 12	65	64	75	52	3.3
HJR	83	27	65	49	1.7
S3	62	32	61	33	0.8
Orthopnea	86	25	66	51	2.1
Edema	41	66	67	40	1.3

- ESCAPE Trial Substudy: 192 pts hospitalized with advanced systolic heart failure → RHC
- History and Physical Exam findings correlating to PCWP >22

Drazner MH. Circ Heart Fail. 2008 Sep;1(3):170-7.

19

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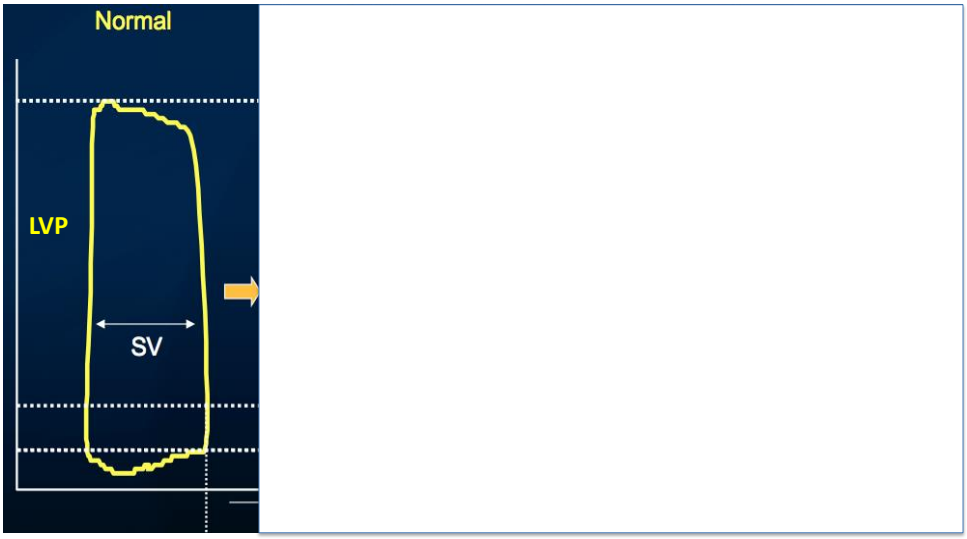
20

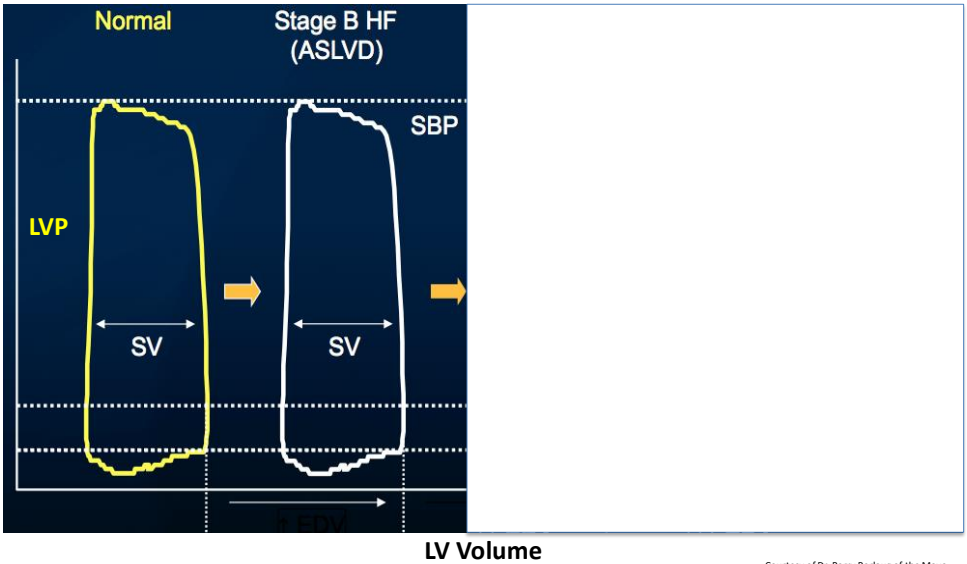
Systolic Dysfunction Stage Progression



Courtesy of Dr. Barry Borlaug of the Mayo Clinic CV Board Review 2014

21

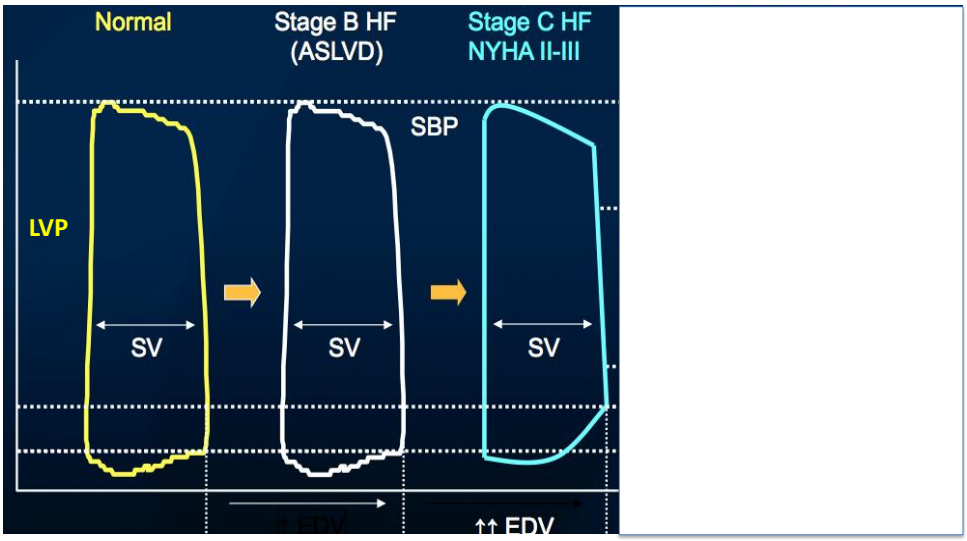
Systolic Dysfunction Stage Progression



Courtesy of Dr. Barry Borlaug of the Mayo Clinic CV Board Review 2014

22

Systolic Dysfunction Stage Progression



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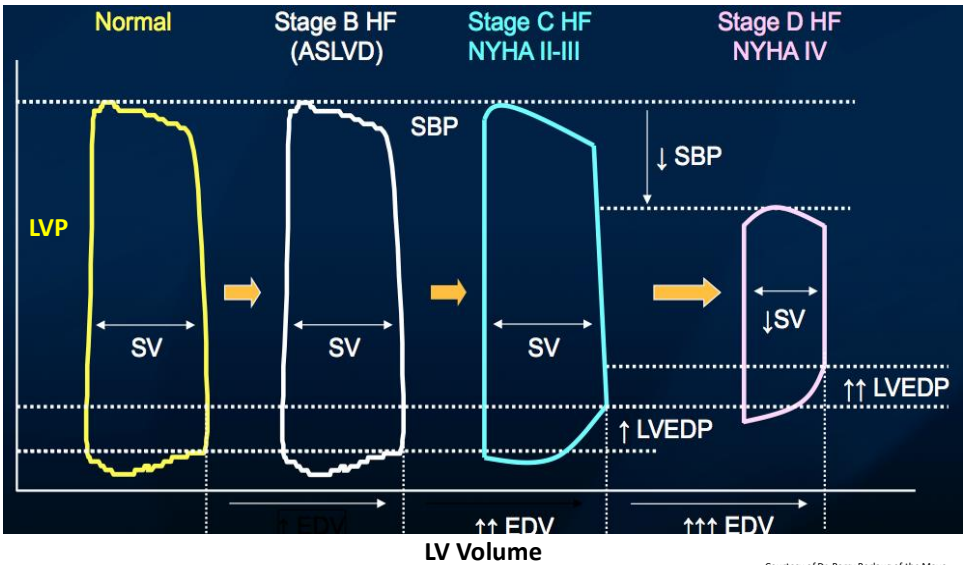
23

Systolic Dysfunction Stage Progression



Courtesy of Dr. Barry Borlaug of the Mayo Clinic CV Board Review 2014

24

Case 2b

Mr. AB as diagnosed with an acute on chronic heart failure exacerbation and admitted to the hospital. An in-hospital echocardiogram revealed slightly larger left ventricular size compared to 4 years ago, and his LVEF dropped to 35%. While hospitalized he was given intravenous diuretics and lost 15 lbs of weight over 3 days. His was euvolemic (normal volume status) on exam and asymptomatic after diuretic treatment. His BP was 140/75 mmHg, HR 68 bpm, normal respiratory rate, and O2 saturation 100% on room air. BNP level dropped to 1700 pg/mL, and renal function normalized.

What Are the Next Best Steps in His Care?

A. Work the patient up for a heart transplant
B. Start a sodium glucose transport protein 2 inhibitor (SGLT2-I), and continue the ACEI and Beta-blocker at current dose
C. Start a mineralocorticoid antagonist (MRA) and an SGLT2-I, change the ACEI to an angiotensin receptor neprilysin inhibitor (ARNI), continue his evidenced based beta blocker, and start an oral diuretic in needed
D. Continue same medications from admission, and repeat echocardiogram in a few months

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https://doi.org/10.1161/CIR.0000000000001063

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

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

27

CHF Treatment – Stage C

MEDICATIONS

- **ARNI** as 1st line treatment
  - Or an ACE-I/ARB's
- Beta-Blockers
- Aldosterone Antagonist
- **SGLT2-I**
- Possibly ISDN/Hydralazine
- Possibly **Ivabradine**
- Possibly Digoxin
- Diuretics if needed

ADDITIONAL TXS

- ICD VS CRT-D
- Cardiac Rehab/Exercise Training
- Consider Referral to Heart Failure Specialist
- Systolic BP Target < **130 mmHg** (Class I, LOE C-EO)

28

ACE Inhibitors

Trial	Entry criteria	Number pts/ duration/ drug	Mortality
CONSENSUS *NEJM* 1987	NYHA IV	253 pts/ 6m Enalapril	↓ 31%
SOLVD-rx *NEJM* 1991	EF <35% and acute CHF (II-III)	2569 pts/ 41m Enalapril	↓ 16%
V-HeFT II *NEJM* 1991	EF <45% and NYHA II-III	804 pts/ 6m-5y Enalapril v I/H	↓ 28% vs isordil/hydral
SOLVD-prev *NEJM* 1992	EF <35% and NYHA I	4228 pts/ 37m Enalapril	↓ 8% NS ↓ 29% death/HF
SAVE *NEJM* 1992	MI w/in 3-16d and EF <40%	2231pts/ 4y Captopril	↓ 19%
AIRE *Lancet* 1993	MI w/in 2-9d and evidence of CHF	1986 pts/ 30m Ramipril	↓ 27%
TRACE *NEJM* 1995	MI w/in 2-6d and EF <35%	1749 pts/ 24m Trandolapril	↓ 24%

29

Angiotensin Receptor Blockers

Trial	Entry criteria	# Patients, Duration, Drug	Mortality
ELITE-II ***Lancet* 2000**	>60y, EF < 40%, NYHA II-IV	3152 pts/ 1.5y Losartan v Captopril	No superiority of one agent over another
Val-HeFT ***NEJM* 2001**	NYHA II-IV, EF < 40% 90% on ACEI	5010 pts/ 2y Valsartan vs placebo	•Similar mortality •CHF hosp: ↓ 27% •↑ death if ACEI/ARB/B
CHARM-added ***Lancet* 2003**	NYHA II-IV EF <40% On an ACEI	2548 pts/ 2y Candesartan vs placebo	• ARB + ACEI ↓ 16% • No incr death in ACEI/ARB/beta
CHARM-altern ***Lancet* 2003**	NYHA II-IV; EF <40% +ACEI intolerant	-2028 pts/ 2y Candesartan vs plac	• ARB ↓ 20%
OPTIMAAL ***Lancet* 2002**	Acute MI and CHF	5477 pts/ 2.7y Valsartan v Captopril	• NS: ACEI better
VALIANT ***NEJM* 2003**	MI w/in 12h-10d + EF < 40% or CHF	14703 pts/ 2y Valsartan vs Captopril vs both	• V vs C: equivalent • V + C: the most adverse events

30

Angiotensin Receptor-Neprilysin Inhibition (ARNI) vs Enalapril in HF: PARADIGM-HF

- 8442 patients
- NYHA Class II-IV, EF < 40%, pro BNP ≥ 600
- Randomized to LCZ696 VS Enalapril
- 1° Endpoint – CV Death, HF hospitalization
- Secondary – Time to death, KCCQ, Time to new A fib, Renal function

NEJM 2014; 371: 993-1004.

31

PARADIGM-HF Exclusion Criteria

- Symptomatic hypotension
- SBP < 100
- Est GFR < 30 or ↓ eGFR of 25 % during run in
- K > 5.2
- Hx ACE/ARB intolerance

NEJM 2014; 371: 993-1004.

32

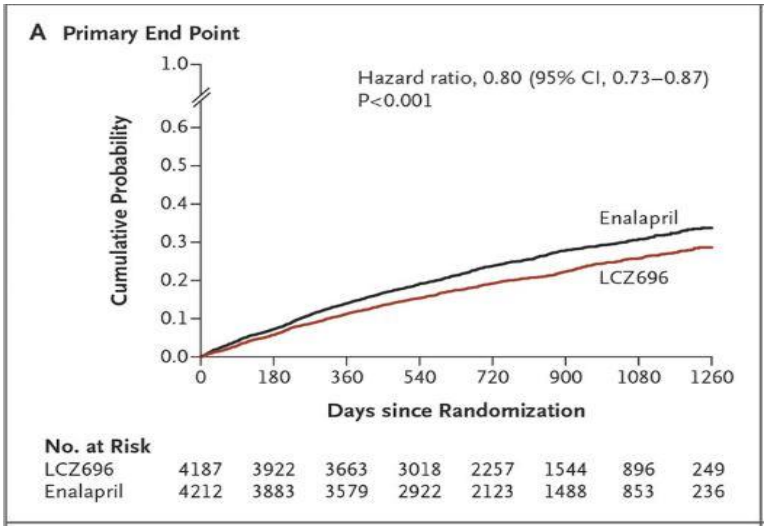
PARADIGM-HF
Study Design

- Switch to Enalapril 10 BID for 2 weeks (10.5% out)
- Then switch to LCZ for tolerability for 4-6 weeks (10.4% out)
- Enalapril held for 1 day prior to switch
- If tolerates both, 1:1 double blind randomization of Enalapril VS Valsartan-Sacubitril

NEJM 2014; 371: 993-1004.

33

CV Death/HF Hospitalization



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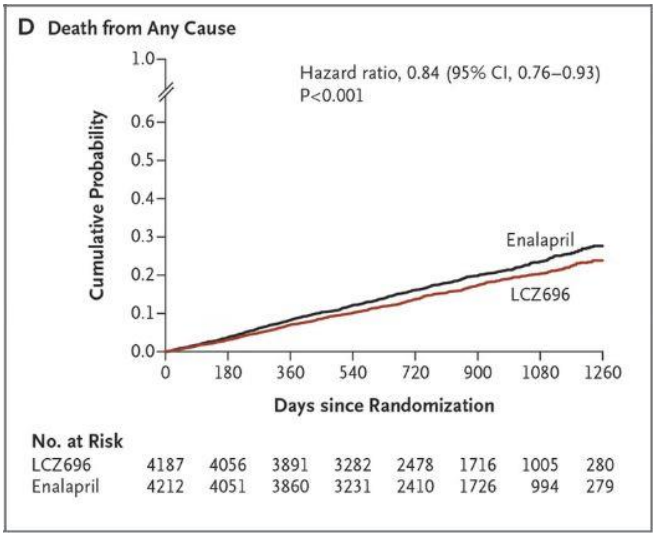
34

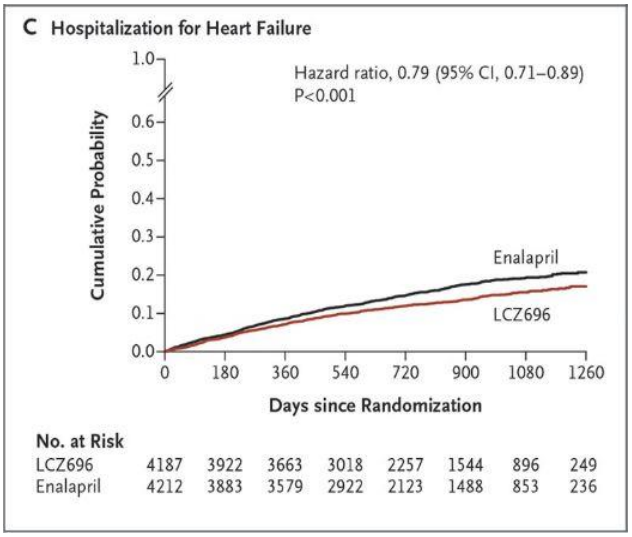
Overall Mortality



NEJM 2014; 371: 993-1004.

35

Heart Failure Hospitalization



NEJM 2014; 371: 993-1004.

36

Adverse Events During Randomized Treatment

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

NEJM 2014; 371: 993-1004.

37

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1-5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6-13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[14-18]
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.[19-25]
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[1-5]
Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.[26-29]

3: Harm	B-R	7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi.[30,31]
3: Harm	C-LD	8. ARNi should not be administered to patients with any history of angioedema.[32-35]
3: Harm	C-LD	9. ACEi should not be administered to patients with any history of angioedema.[36-39]

38

Beta Blockers

Trial	Entry Criteria	# pts/ dur/ drug	Mortality
US Carvedilol HF Study Group *Circulation* 1996	NYHA II-III and EF < 35%	1094 pts/ 6-12m Carvedilol	↓ 48% in death/hosp/incr meds
CIBIS-II *Lancet* 1999	NYHA III-IV and EF < 35%	2647 pts/ 1.3y Bisoprolol	↓ 32%
MERIT-HF *JAMA* 2000	NYHA II-III and EF < 40%	3991 pts/ 1y Metoprolol XL	↓ 19%
COPERNICUS *NEJM* 2001	NYHA IV and EF < 25%	2289 pts/ 10.4m Carvedilol	↓ 35%
CAPRICORN *Lancet* 2001	MI 3-21d, EF < 40%, on ACEI	1959 pts/ 1.3y Carvedilol	↓ 23%
COMET *Lancet* 2003	NYHA II-IV and EF < 35%	3029 pts/ 4.8y Carved vs metop	↓ 17% in carvedilol

39

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendation
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.[4–8]

40

Aldosterone Antagonists

Trial	Entry criteria	Number pts/ dur/ drug	Mortality
RALES *NEJM* 1999	NYHA III-IV EF <35%, on ACEI and loop	1663 pts/ 2y Spironolactone	↓ 30%
EPHESUS *NEJM* 2003	Acute MI + EF < 40% + CHF sx and/or DM	6642 pts/ 16m Eplerenone	↓ 15%
EMPHASIS *NEJM* 2011	NYHA II, <=30% + CHF sx	2737 pts/ 21m Eplerenone	↓ 18%

Yancy C et al. Circulation 2013;128:e240-e327

41

Aldosterone Antagonists

- For patients with EF ≤35%, NYHA class II- IV, in addition to ACE-I, beta-blocker, loop diuretics
- Post-MI patients with clinical HF or DM and LVEF<40% who are on standard therapy including ACE-I or ARB
- Avoid if K > 5.0 or Cr > 2.5 (clearance <30mL/min)

Yancy C et al. Circulation 2013;128:e240-e327

42

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.[4–7]
3: Harm	B-NR	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.[8,9]

43

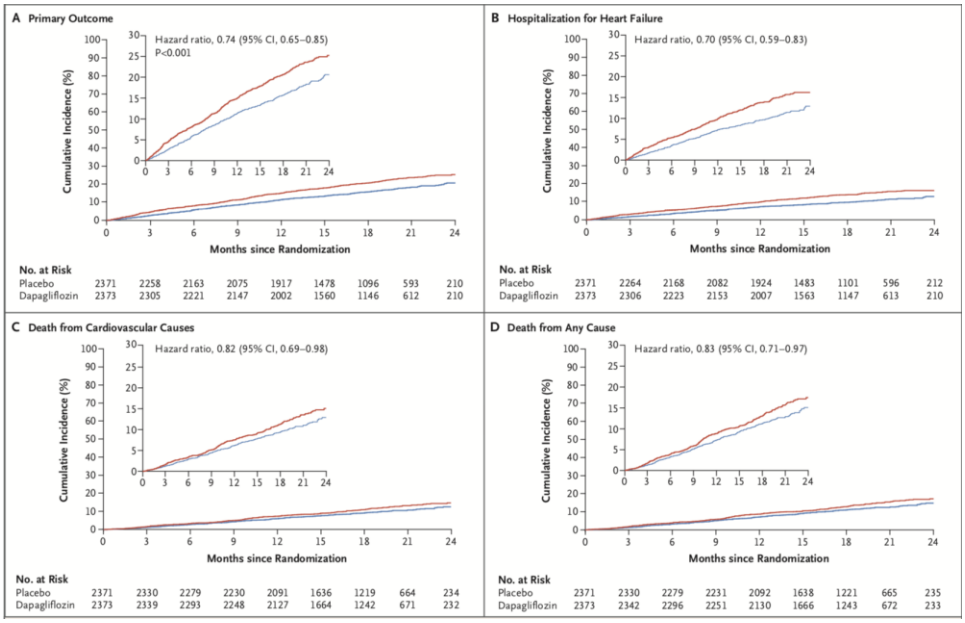
ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

N=4744
NYHA II-IV
EF ≤40%
Elevated levels of natriuretic peptides
42% had T2DM
48% had prior hx of HF hospitalization

44



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EMPEROR Reduced

METHODS

- 3730 pts
- LVEF ≤ 40%
- NYHA Class II – IV
- Median 16 months
- 1 Endpoint: Composite CV Death & HHF or urgent/emergent HF visit requiring IV tx

46

EMPEROR Reduced

METHODS

- 3730 pts
- LVEF ≤ 40%
- NYHA Class II – IV
- Median 16 months
- 1 Endpoint: Composite CV Death & HHF or urgent/emergent HF visit requiring IV tx

RESULTS

Treatment VS Placebo

- **1 Endpoint: 19.4% (361 of 1863 pts) VS 24.7% (462 of 1867 pts)** HR 0.75; 95% CI 0.65 to 0.86; P<0.001
- **HHF: 388 VS 553 events** (HR 0.70; 95% CI 0.58 to 0.85; P<0.001)

47

EMPEROR Reduced

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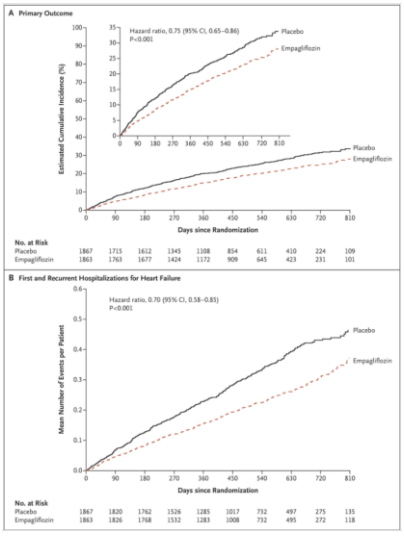


48

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[1,2]
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[3,4]

49

Hydralazine/Isosorbide Dinitrate

Trial	Entry criteria	Number pts/ dur/ drug	Endpoints
V-HeFT I NEJM 1986	EF <45% and NYHA II-III	642 pts/ 2y I/H vs prazosin vs placebo	↓ 34% mortality I/H vs placebo No diff prazosin vs placebo
V-HeFT II NEJM 1991	EF <45% and NYHA II-III	804 pts/ 6m-5y Enalapril vs I/H	↓ 28% mortality vs isordil/hydral
A-HeFT NEJM 2004	EF ≤ 35% and NYHA III-IV and black (90% ACEI/ARB, 70% BB)	1050 pts/ 18m I/H vs placebo	↓ 39% all-cause mortality ↓ 33% hospitalization ↑ QOL 6m

Yancy C et al. Circulation 2013;128:e240-e327

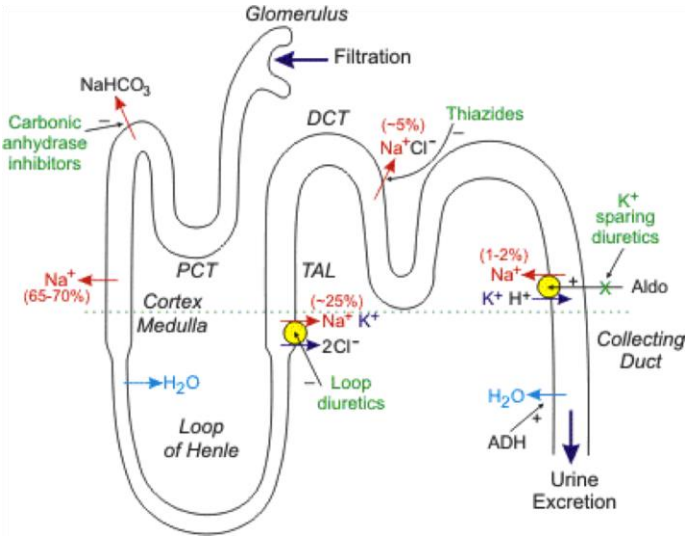
50

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
1	A	1. For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.[1,2]
Value Statement: High Value (B-NR)		2. For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy with ACEi or ARB, beta blockers, and MRA, the combination of hydralazine and isosorbide dinitrate provides high economic value.[3]
2b	C-LD	3. In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.[4,5]

51

Diuretics



52

Diuretics

Loop Diuretics

- **Furosemide, Bumetanide, Torsemide**

Early distal tubule

- Metolazone, Chlorthalidone, HCTZ, chlorothiazide

Late distal tubule

- Spironolactone, Eplerenone (K+ sparing)

Yancy C et al. Circulation 2013;128:e240-e327

53

Ivabradine

- Specific inhibitor of the I_f current of the SA
- Does not affect contractility
- Significantly lowers heart rate

Lancet 2010: 376: 875-85.

54

SHIFT Trial - Ivabradine

- 6558 patients
- Randomized, DB, PC
- Symptomatic HF, heart rate > 70
- HF admission within prior year
- On stable Beta-Blocker
- Primary endpoint- CV death, HF hospitalization

Lancet 2010: 376: 875-85.

55

SHIFT Results

Endpoints	Hazard ratio	95% CI	*p* value
Primary composite endpoint (CV death or hospital admission for worsening HF)	0.82	[0.75;0.90]	*p*<0.0001
All-Cause Mortality	0.90	[0.80;1.02]	*p*=0.092
Death from heart failure	0.74	[0.58;0.94]	*p*=0.014
All-cause hospital admission	0.89	[0.82;0.96]	*p*=0.003
Any CV hospital admission	0.85	[0.78;0.92]	*p*=0.0002
CV death/hospital admission for HF or non-fatal MI	0.82	[0.74;0.89]	*p*<0.0001

2010;376(9744):875-885 www.shift-study.com

56

SHIFT Results

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2010;376(9744):875-885 www.shift-study.com

57

Adverse Events

	Patients with an adverse event			Patients with an adverse event leading to drug withdrawal		
	Ivabradine group (n=3232)	Placebo group (n=3260)	p value	Ivabradine group (n=3232)	Placebo group (n=3260)	p value
All	2439 (75%)	2423 (74%)	0·303	467 (14%)	416 (13%)	0·051
Heart failure	804 (25%)	937 (29%)	0·0005	70 (2%)	82 (3%)	0·367
Symptomatic bradycardia	150 (5%)	32 (1%)	<0·0001	20 (1%)	5 (<1%)	0·002
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0·0001	28 (1%)	5 (<1%)	<0·0001
Atrial fibrillation	306 (9%)	251 (8%)	0·012	135 (4%)	113 (3%)	0·137
Phosphenes*	89 (3%)	17 (1%)	<0·0001	7 (<1%)	3 (<1%)	0·224
Blurred vision	17 (1%)	7 (<1%)	0·042	1 (<1%)	1 (<1%)	1·000

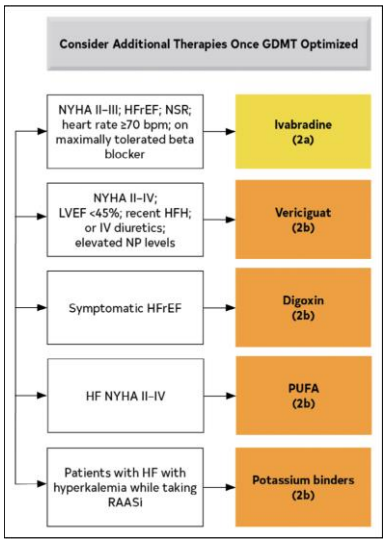
Data are number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients.

*Transient enhanced brightness in a restricted area of the visual field.

Lancet 2010: 376: 875-85.

58

2022 ACC/AHA/HFSA Guidelines



59

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
3: No Benefit	A	1. In patients with HFrEF, dihydropyridine calcium channel-blocking drugs are not recommended treatment for HF.[1,2]
3: No Benefit	B-R	2. In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies.[3–9]
3: Harm	A	3. In patients with HFrEF, nondihydropyridine calcium channel-blocking drugs are not recommended.[10–13]
3: Harm	A	4. In patients with HFrEF, class IC antiarrhythmic medications and dronedarone may increase the risk of mortality.[14–16]
3: Harm	A	5. In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations.[17–21]
3: Harm	B-R	6. In patients with type 2 diabetes and high cardiovascular risk, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin increase the risk of HF hospitalization and should be avoided in patients with HF.[22–24]
3: Harm	B-NR	7. In patients with HFrEF, NSAIDs worsen HF symptoms and should be avoided or withdrawn whenever possible.[25–28]

60

NNT All Cause Mortality HFrEF

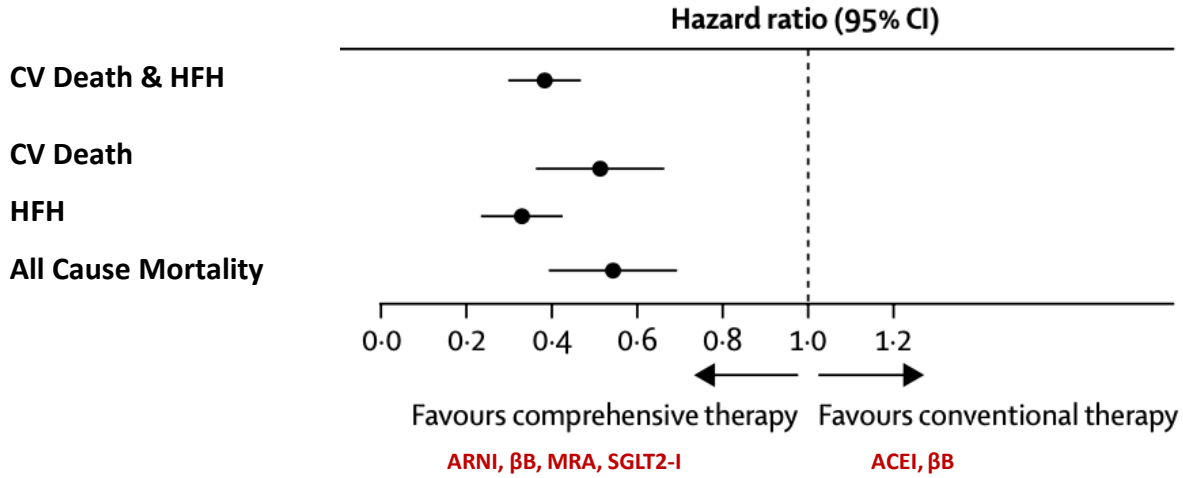
Table 15. Benefits of Evidence-Based Therapies for Patients With HFrEF[3–6,8,10–14,23,31–42]

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

Heidenreich et al Circ 2022

61

Long-term Overall Survival with Comprehensive Disease-Modifying Therapy vs Conventional Therapy



Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet. 2020 Jul 11;396(10244):121-128. doi: 10.1016/S0140-6736(20)30748-0. Epub 2020 May 21. PMID: 32446323.

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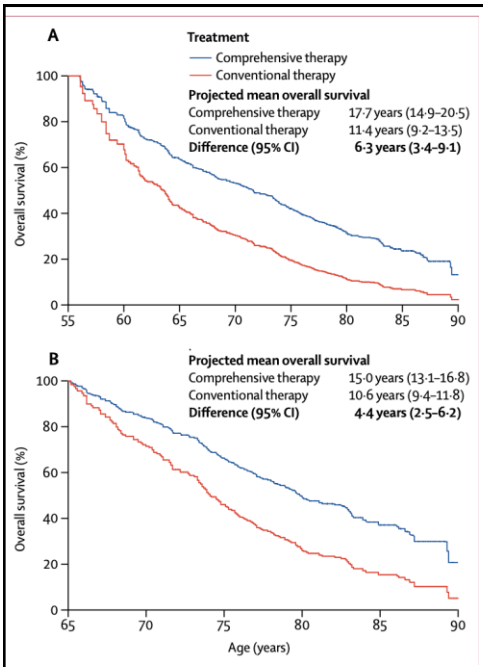

Overall KM Estimated Survival Curves for Comprehensive Therapy (ARNI, βB, MRA, SGLT2-I) VS Conventional Therapy (ACEI & βB)

Residual Lifespan

Started at age 55

- **6.3 years**

Started at age 65

- **4.4 years**

Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet. 2020 Jul 11;396(10244):121-128. doi: 10.1016/S0140-6736(20)30748-0. Epub 2020 May 21. PMID: 32446323.

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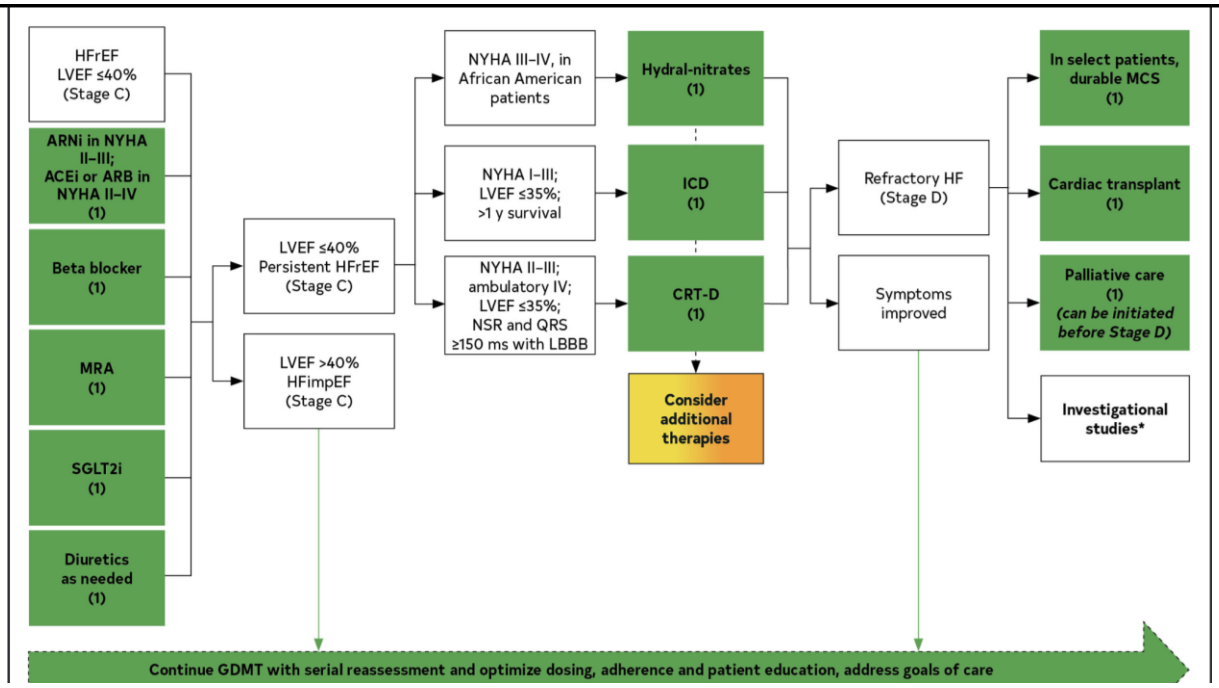
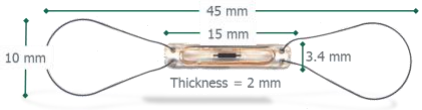
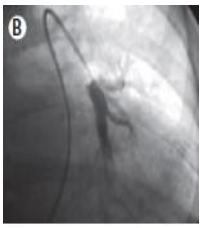


Heidenreich et al Circ 2022

64

CHAMPION TRIAL





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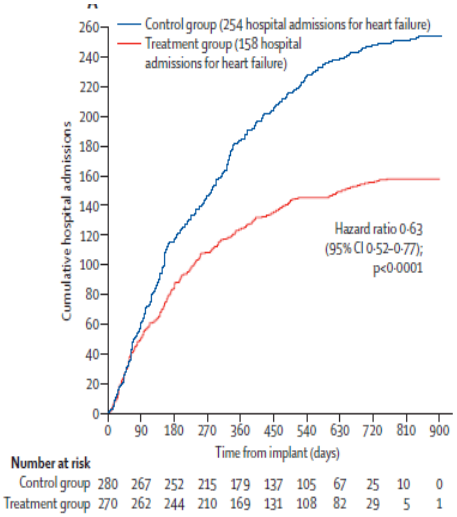
CHAMPION Trial – HF Hospitalization



Lancet 2011;377:658-66

66

CHAMPION – Results

	Not enrolled (n=25)	Treatment group (n=270)	Control group (n=280)	All patients (n=575)	Risk (95% CI)	p value	NNT
Primary efficacy endpoints*							
Heart-failure-related hospitalisations up to 6 months (number; events per patient per 6 months)	NA	84 (0·32)	120 (0·44)	NA	0·72† (0·60–0·85)	0·0002	8
Primary safety endpoints‡							
Device-related or system-related complications	2 (8%)	3 (1%)	3 (1%)	8 (1%)	§	<0·0001	NA
Pressure-sensor failures	0	0	0	0	§	<0·0001	NA
Prespecified supplementary efficacy endpoints¶							
Heart-failure-related hospitalisations during entire randomised follow-up	NA	158	254	NA	0·63† (0·52–0·77)	<0·0001	4
Secondary efficacy endpoints							
Change from baseline in pulmonary artery mean pressure at 6 months (mm Hg×days; mean area under the curve)	NA	−156	33	NA	NA	0·008	NA
Patients admitted to hospital for heart failure at 6 months	NA	55 (20%)	80 (29%)	NA	0·71‖ (0·53–0·96)	0·03	NA
Days alive outside hospital at 6 months (mean, SD)	NA	174·4 (31·1)	172·1 (37·8)	NA	NA	0·02	NA
Minnesota Living with Heart Failure Questionnaire at 6 months (mean, SD)	NA	45 (26)	51 (25)	NA	NA	0·02	NA

Lancet 2011;377:658-66

67

GUIDE-HF

Full Study Results

Pre-COVID

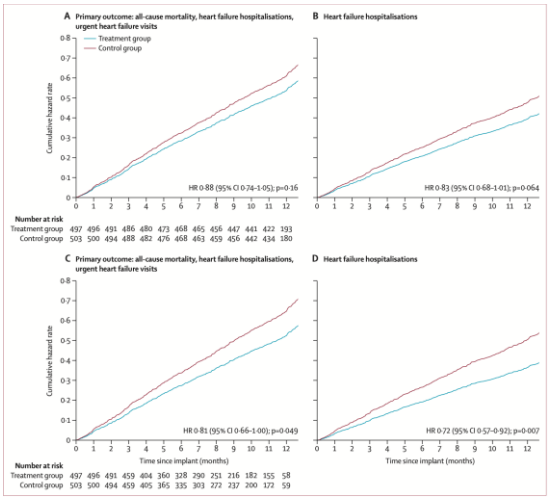


Figure 2: Cumulative hazard rate curves and 95% CIs for the primary composite endpoint and heart failure hospitalisations
(A) Overall analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure hospital visits. (B) Overall analysis—heart failure hospitalisations. (C) Pre-COVID-19 impact analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure visits. (D) Pre-COVID-19 impact analysis—heart failure hospitalisations. HR=hazard ratio.

68

PA Sensor Monitoring

Recommendation for Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	1. In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.[1–4]
Value Statement: Uncertain Value (B-NR)		2. In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PA pressure by an implanted hemodynamic monitor provides uncertain value.[4–7]

69

Case 3

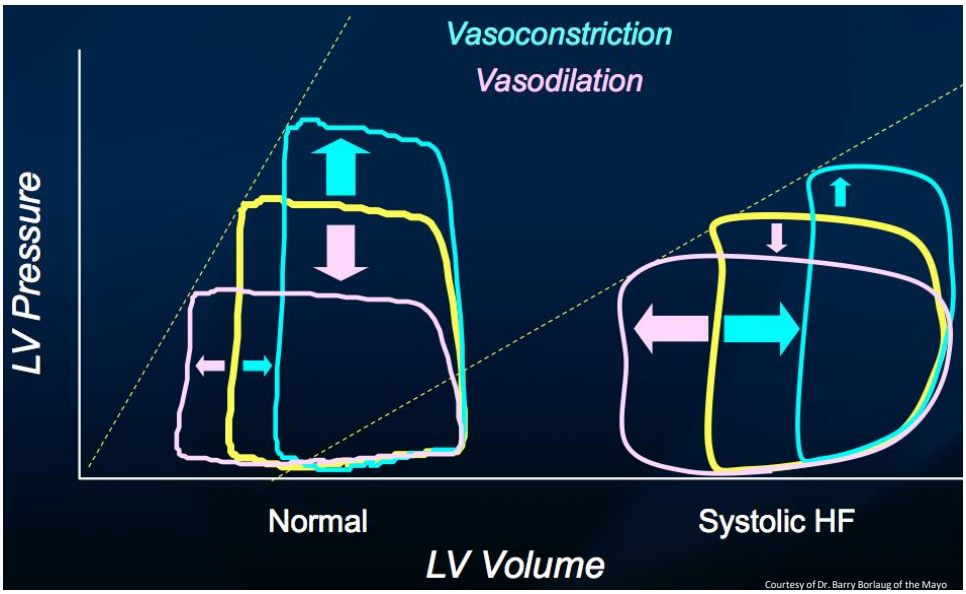
Mr. AB is a now a 40 y/o man with history of Stage C Heart failure with reduced ejection fraction. Over the last 4 years the patient had a defibrillator placed for primary prevention of sudden cardiac death, but was otherwise stable on his medical regimen of an ARNI, MRA, beta-blocker, and SGLT2-I. However, over the past year he has not been able to tolerate his medication dosages due to episodes of symptomatic hypotension acute kidney injuries. Currently he is only able to tolerate his SGLT2-I, a low dose beta-blocker, a loop diuretic, and an MRA. His ARNI was discontinued due to repeated hypotension episodes. He is not complaining of any current light-headedness. In your office today he reports being easily fatigued with minimal exertion. He endorses shortness of breath with laying flat for more than 1 hour. He has had a 10 lb unintentional weight loss over the last 6 months with poor appetite due to feeling nauseated. On physical exam his pulse rate is 50 bpm, but you auscultate a heart rate of 100 bpm. His arms and legs are very cold to touch, but his lungs are clear, jugular pressure is mildly elevated, and there is no peripheral edema. You send the patient to the emergency department due his symptoms with concerns of cardiogenic shock.

In the emergency department, the patient's vital signs reveal a blood pressure of 92/58 mmHg, HR 100 bpm, normal respiratory rate, and normal O2 saturations.

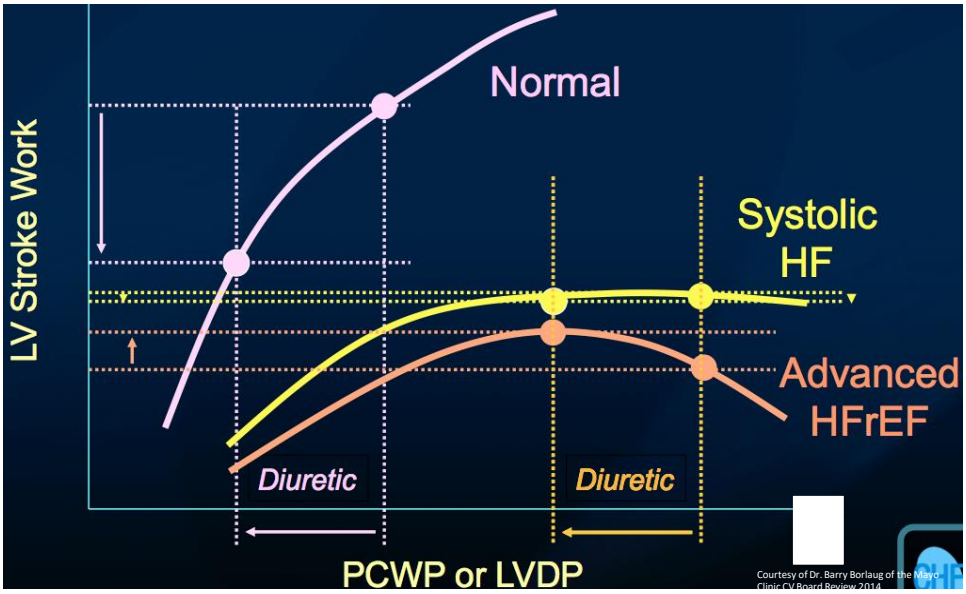
What Are the Next Best Steps?

A. Start the patient on a vasopressor such as norepinephrine to improve his BP
B. Hold off starting intravenous diuretics because the patient has low blood pressure
C. Place a pulmonary artery catheter (Swan), start therapies based on the patient's hemodynamics
D. Increase the patient's beta blocker dose to better control the tachycardia

Afterload Sensitivity of HFrEF



Preload Sensitivity of HFrEF



73

JACC: HEART FAILURE VOL. 8, NO. 11, 2020

PUBLISHED BY ELSEVIER

Complete Hemodynamic Profiling With Pulmonary Artery Catheters in Cardiogenic Shock Is Associated With Lower In-Hospital Mortality

A. Reshad Garan, MD, MS,[a,*] Manreet Kanwar, MD,[b,*] Katherine L. Thayer, MPH,[c] Evan Whitehead, MD,[d] Elric Zweck, MSc,[c,e] Jaime Hernandez-Montfort, MD, MPH,[f] Claudius Mahr, DO,[g] Jillian L. Haywood, MS,[c] Neil M. Harwani, MS,[c] Detlef Wencker, MD,[h] Shashank S. Sinha, MD, MSc,[i] Esther Vorovich, MD,[j] Jacob Abraham, MD,[k] William O'Neill, MD,[l] Daniel Burkhoff, MD, PhD,[m] Navin K. Kapur, MD[c]

74

Cardiogenic Shock Working Group

METHODS

- The Cardiogenic Shock Working Group (CSWG) collected retrospective data in CS patients from 8 tertiary care institutions from 2016 - 2019
- Patients were divided by SCAI stages and outcomes analyzed by the PAC-use group prior to initiating mechanical circulatory support (MCS)
- PAC Use Groups
  - No PAC Data
  - Incomplete PAC Data
  - Complete PAC Data

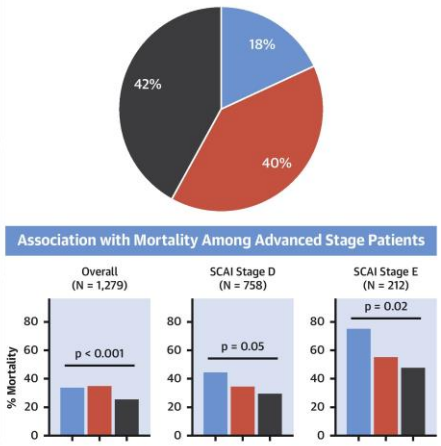
Garan et al JACC HF 2020

75

75

CENTRAL ILLUSTRATION: Frequency of Mortality Among PAC Use Overall and by SCAI Stage

PAC Utilization	Study Definition
None	Presence of **NONE** of the following invasive hemodynamics: • Pulmonary Artery Systolic Pressure • Pulmonary Artery Diastolic Pressure • Pulmonary Capillary Wedge Pressure • Pulmonary Artery Saturation • Right Atrial Pressure
Incomplete Assessment	Presence of **1-4** of the following invasive hemodynamics: • Pulmonary Artery Systolic Pressure • Pulmonary Artery Diastolic Pressure • Pulmonary Capillary Wedge Pressure • Pulmonary Artery Saturation
Complete Assessment	Presence of **ALL** of the following invasive hemodynamics: • Pulmonary Artery Systolic Pressure • Pulmonary Artery Diastolic Pressure • Pulmonary Capillary Wedge Pressure • Pulmonary Artery Saturation **AND** presence of Right Atrial Pressure



Garan, A.R. et al. J Am Coll Cardiol HF. 2020;8(11):903-13.

76

CENTRAL ILLUSTRATION: Frequency of Mortality Among PAC Use Overall and by SCAI Stage

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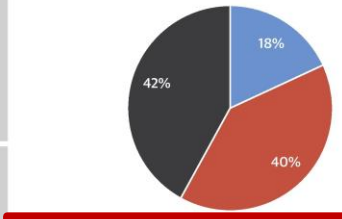
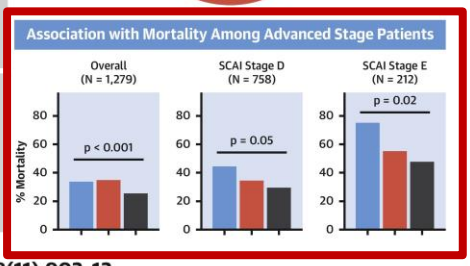




Garan, A.R. et al. J Am Coll Cardiol HF. 2020;8(11):903-13.

The complete PAC assessment group had the lowest in-hospital mortality than the other groups across all SCAI stages

No PAC assessment was associated with higher in-hospital mortality than complete PAC assessment in the overall cohort (adjusted odds ratio = 1.57; 95% CI 1.06 to 2.33)

77

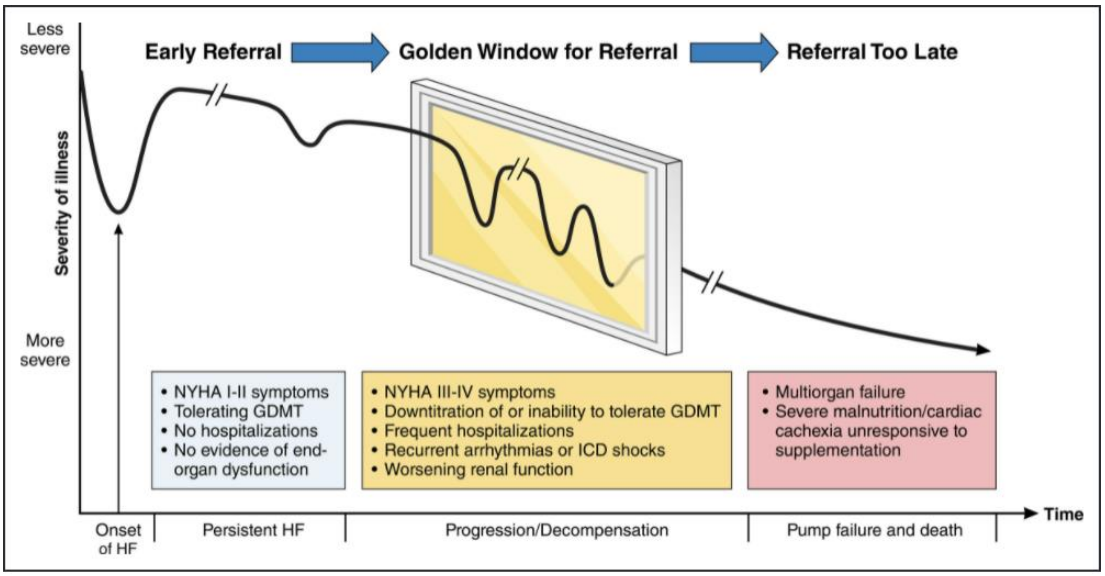
ACC/AHA/HFSA 2022 Heart Failure Guidelines

Recommendations for Evaluation and Management of Cardiogenic Shock
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	1. In patients with cardiogenic shock, intravenous inotropic support should be used to maintain systemic perfusion and preserve end-organ performance.[1-8]
2a	B-NR	2. In patients with cardiogenic shock, temporary MCS is reasonable when end-organ function cannot be maintained by pharmacologic means to support cardiac function.[9-17]
2a	B-NR	3. In patients with cardiogenic shock, management by a multidisciplinary team experienced in shock is reasonable.[17-22]
2b	B-NR	4. In patients presenting with cardiogenic shock, placement of a PA line may be considered to define hemodynamic subsets and appropriate management strategies.[23-27]
2b	C-LD	5. For patients who are not rapidly responding to initial shock measures, triage to centers that can provide temporary MCS may be considered to optimize management.[17-22]

78

78



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79

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American Heart Association.

AHA SCIENTIFIC STATEMENT

Guidance for Timely and Appropriate Referral of Patients With Advanced Heart Failure: A Scientific Statement From the American Heart Association

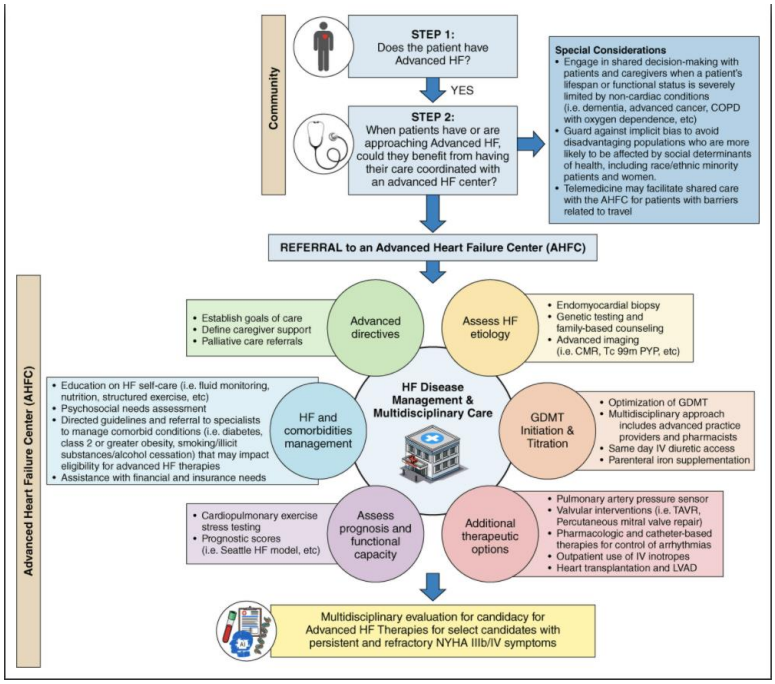
Alanna A. Morris, MD, MSc, FAHA, Chair, Prateeti Khazanie, MD, MPH, Vice Chair, Mark H. Drazner, MD, MSc, Vice Chair, Nancy M. Albert, PhD, Khadijah Breathett, MD, MS, FAHA, Lauren B. Cooper, MD, MHS, Howard J. Eisen, MD, Patrick O'Gara, MD, Stuart D. Russell, MD, and on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Hypertension

80

Table 1. Clinical Clues to Help Identify Patients With Advanced HF (Table view)

Inotrope dependence
LVEF ≤25%, particularly with high-risk features on echocardiogram (grade III or IV diastolic dysfunction; significant RV dysfunction; high pulmonary artery pressures or severe MR despite attempts at decongestion)
≥2 Hospitalizations or emergency department visits for decompensated HF in 12 mo
Persistent NYHA class III or IV symptoms, including fatigue and confusion
High-risk biomarker profile (eg, hyponatremia, very elevated natriuretic peptides or troponin)
Escalating doses of diuretics (eg, >160 mg/d furosemide) or persistent edema despite escalating diuretic doses
Downtitration of GDMT as a result of hemodynamic intolerance such as hypotension (SBP <90 mm Hg), dizziness, excessive fatigue, or nausea
Discontinuation of ACE inhibitor/ARB/ARNI because of hypotension or renal intolerance
Progressive renal failure with rising creatinine/BUN
Recurrent atrial fibrillation or VT with ICD shocks
Nonresponse to cardiac resynchronization therapy
Cardiac cachexia (ie, unintentional loss of >5% of body weight attributable to HF)
High mortality risk from validated risk prediction models or calculators

81



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82

Summary

- Heart disease remains the #1 cause of death in the US and HF is the deadliest CV condition
- Comprehensive therapy with ARNI, BB, MRA, SGLT2-I improves survival
- Recognize the signs and symptoms of CHF exacerbation and cardiogenic shock
- Have a low threshold to refer to Advanced HF Cardiologists