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University of California, Irvine
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Physician Referral
1-877- UCI-DOCS
(824-3627)

Advanced Heart Failure & VAD Referral
714-UC-HEART (714-824-3278)

Dawn Lombardo, DO, MS

Medical Director: UC Irvine Health's Advanced Heart Failure & Left Ventricular Assist Device (VAD) Program

Specialty:	Cardiology
Medical Degree:	Chicago College of Osteopathic Medicine
Residency:	Northwestern Hospital
Fellowship	Cardiology: University of Illinois at Chicago
Sub-Specialty:	Advanced Heart Failure & Cardiac Transplantation: University of California, San Diego
Master of Science:	Organic Chemistry
Undergraduate:	Mfg Engineering & Software Systems
Office Location:	UC Irvine Medical Center The City Tower, Suite 414 Orange, CA

Academic Distinctions
Diplomate of American Board of Internal Medicine
Diplomate in Cardiovascular Disease
Diplomate of American Board of Echocardiography

Research Interests
- Advanced Heart Failure; Strain Imaging
- Cardiomyopathies: Rare Storage Diseases, Neuromuscular
- Cardio-Oncology
- Women's Heart Disease

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Heart Failure Management

Dawn Lombardo, DO, MS
HS Clinical Professor of Medicine
University of CA, Irvine
DOM|Division of Cardiology
Medical Director|Advanced HF & VAD Program

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Disclosures

- None

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Learning Objectives

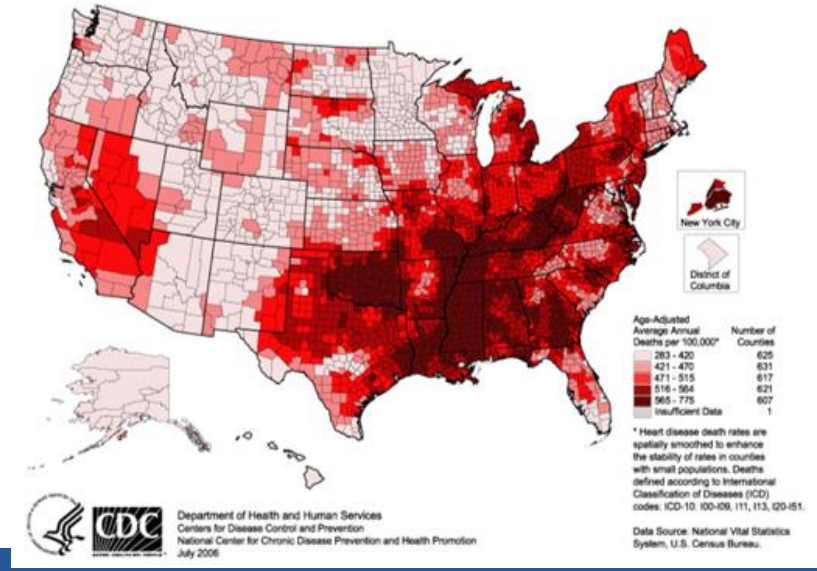
1. Heart Failure Demographics/Epidemiology

2. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

3. 2021 Update to The 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues about Heart Failure with Reduced Ejection Fraction (HFrEF)

Heart Failure in the United States

- Prevalence 2013-2016 6.2 million Americans
- Projections:
  - HF prevalence will increase 46% from 2012-2030 ~ 8 million people >=18y/o with HF
  - Lifetime risk for HF 20-45% at age 45 y/o – 95 y/o
  - Lifetime risk for HF occurring for people with BP> 160/90mmHg is 1.6X's of those with BP<120/90mmHg
- Traditional risk factors account for considerable proportion of HF risk: CHD, HTN, DM, obesity, smoking are responsible for 52% of incident HF cases
  - At least 1 HF risk factor is present in up to 1/3 of the US adult populations
  - Healthy dietary and lifestyle factors (normal weight, no tob, regular physical activity, moderate alcohol intake, consumption of breakfast cereals/fruits/vegetables) were related to lower risk of HF
- Non-traditional risk factors: laboratory (BNP, IL6, CRP, Cr, high HCT, low HgB, albumin, hs-trop), PVCs, FEV1/FVC, SES, LV function, FHx & genetics
- 1,000,000 new HF diagnoses annually
  - 300,000 – 800,000 Americans with advanced heart failure
- 809,000 hospital discharges with primary HF/year
  - If HF diagnosis → 83% w/at least 1 hospitalization and 43% hospitalized at least 4 times!
  - 932,000 physician office visits with primary diagnosis of HF
- Overall mortality ~ 29.6% at 1 year and 50% at 5 years
  - Mortality after AHF hospitalization at 30-day = 10.4%, 1-year = 22% and 1-year = 42.3%
- $30.7 billion 2012 → $69.8 billion in 2030 (127% increase) which is ~ $244/every US adult
  - 50% 2/2 HF hospitalizations



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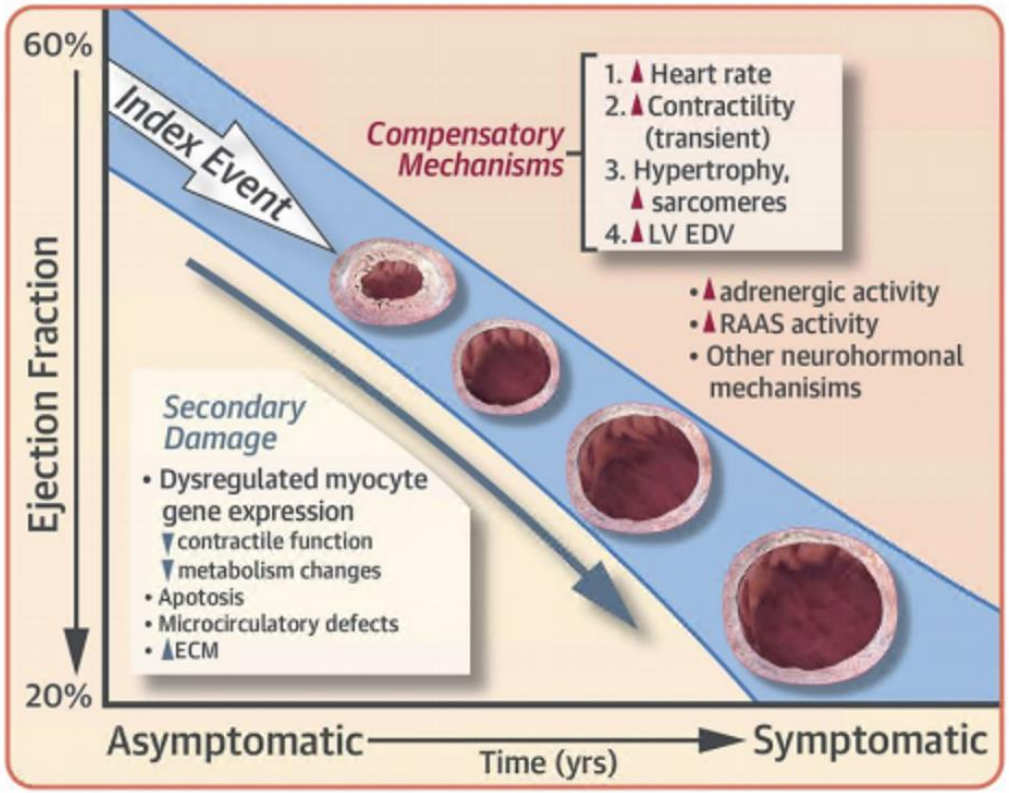
CENTRAL ILLUSTRATION: Natural History of HFrEF Phenotype



Bristow, M.R. et al. J Am Coll Cardiol HF. 2017;5(11):772-81.

Michael R. Bristow et al. JCHF 2017;5:772-781

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JACC Heart Failure

American Heart Association.

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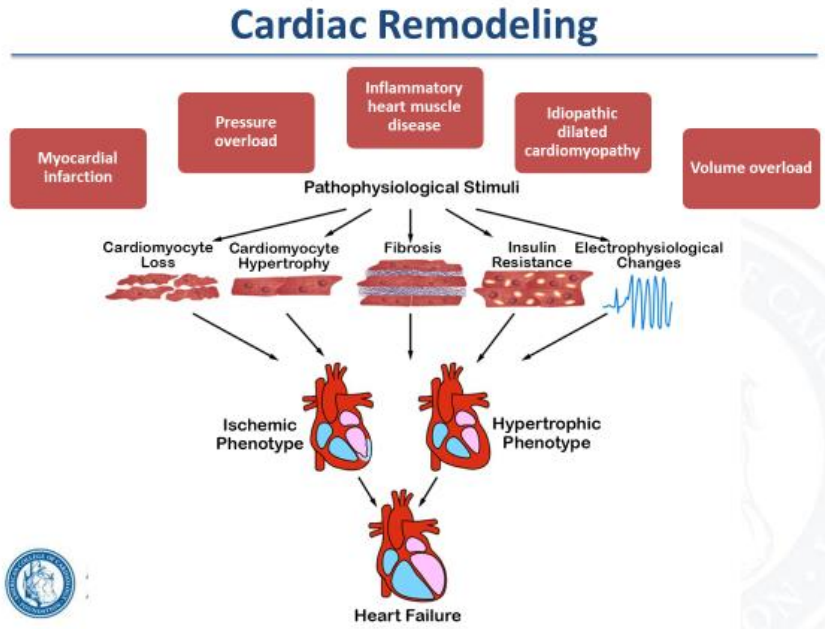
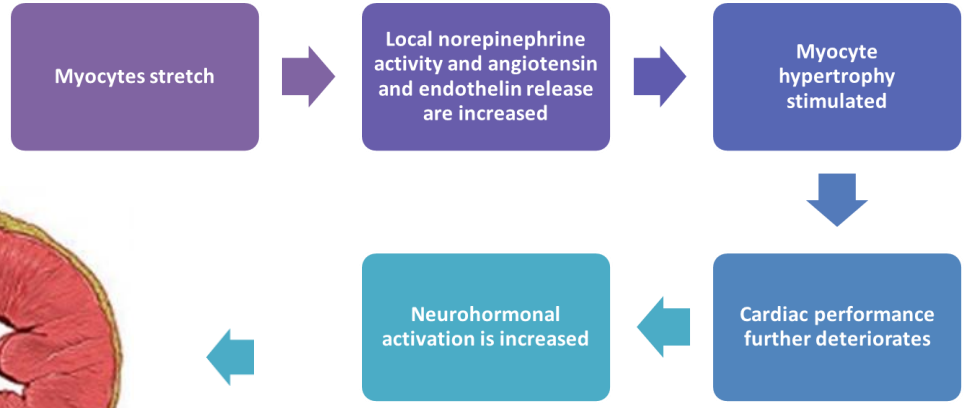
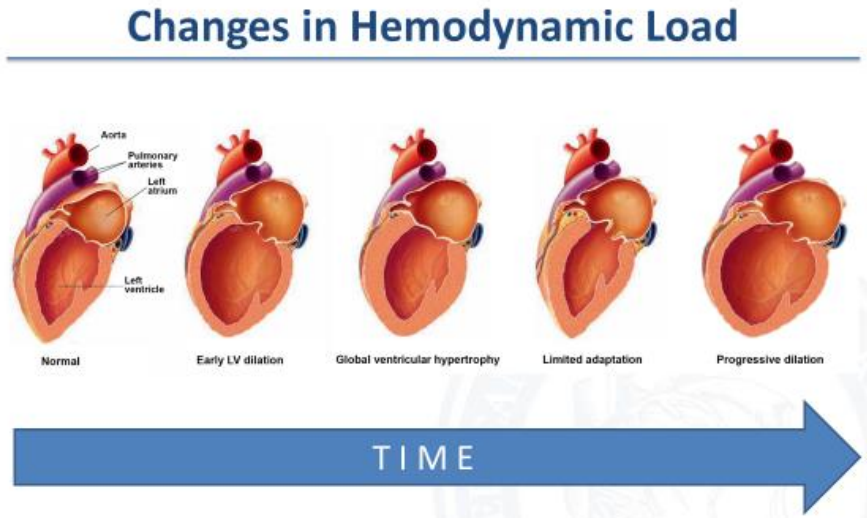
Process of cardiac remodeling involves neurohormonal activation (SNS, RAAS, Endothelin,…adverse cardiac remodeling







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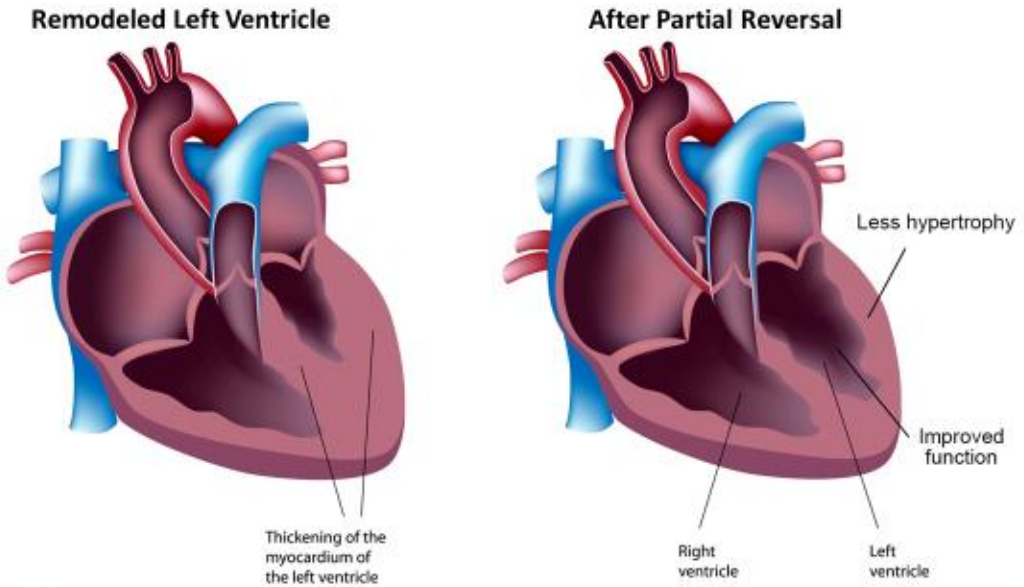
Reverse Cardiac Modeling



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Reverse Cardiac Modeling

Clinical Therapies that Reverse Cardiac Remodeling

- ß-blockers
- Pacing both ventricles
- Physical devices that control diastolic filling
- ACE inhibitors and angiotensin-receptor blockers
- Aldosterone or corticosteroid inhibitors
- Therapies that affect cardiac cells
- LV assist devices
- Nitric oxide plus hydralazine (vasodilators)
- Ventriculoplasty (surgical repair of a defect in the LV)

Clinical Therapies that have Not Shown to Reverse Cardiac Remodeling

- Thiazide diuretics
- Calcium channel blockers
- Digoxin

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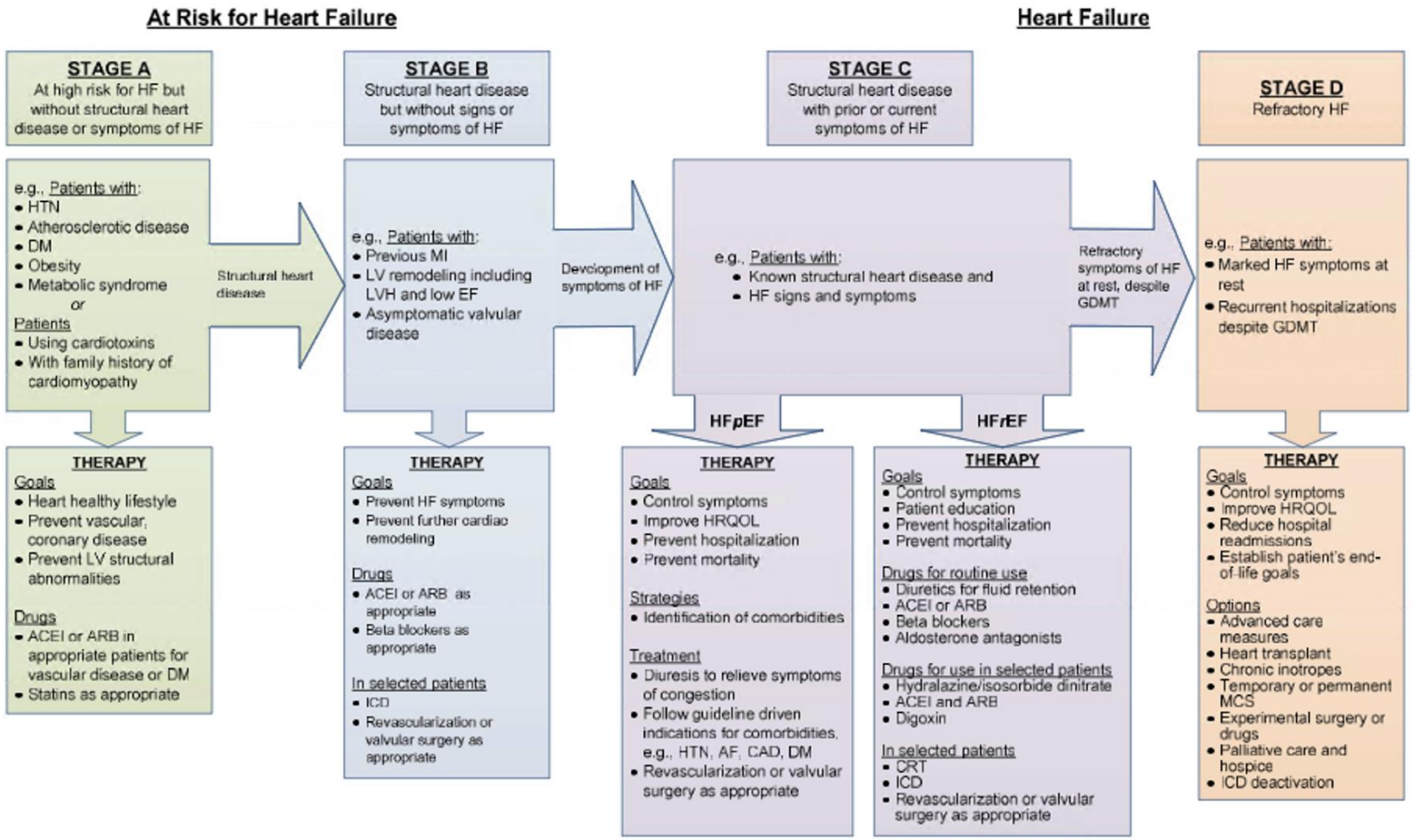
Stages, Phenotypes and Treatment of HF



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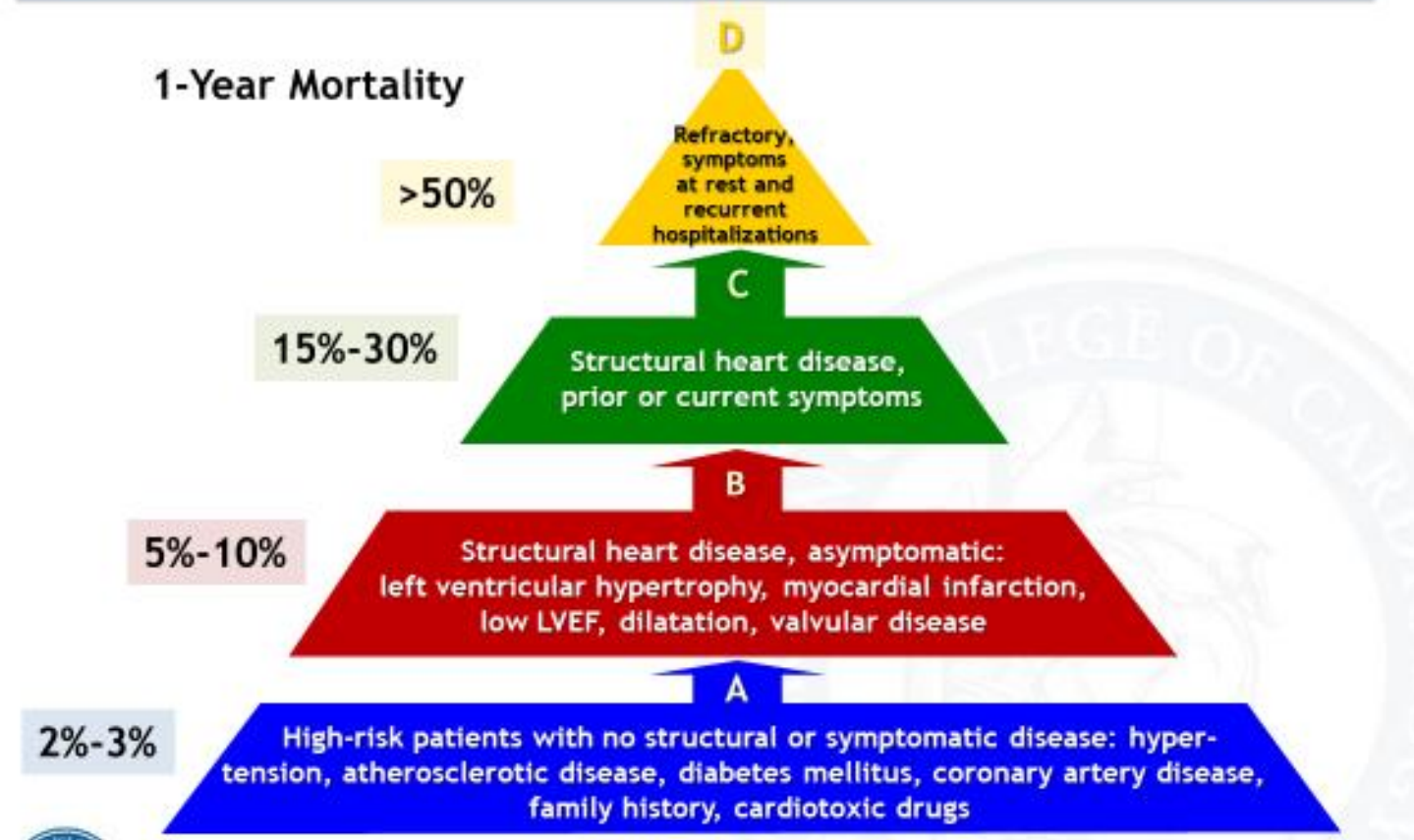
ACCF/AHA HF Staging



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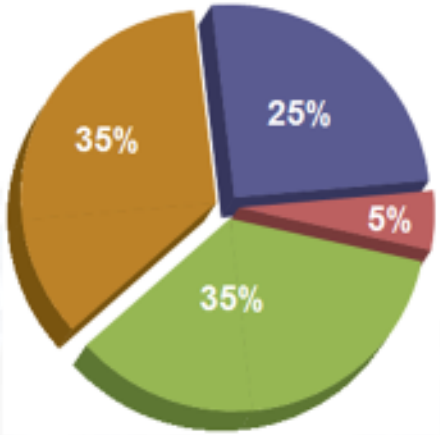
Hunt SA et al. J Am Coll Cardiol 2009;53;e1-e90.

New York Heart Association (NYHA) Classification of HF

Class	Description
I	Patient has no limitation of physical activity. No symptoms arise from ordinary physical activity.
II	Patient has slight limitation of physical activity due to mild symptoms (fatigue, shortness of breath, palpitations and/or angina) during ordinary activity. Patient is comfortable at rest.
III	Patient has marked limitation of physical activity due to symptoms even at less-than-ordinary activity. Patient is comfortable at rest.
IV	Patient is unable to do any physical activity without discomfort. Symptoms experienced at rest.



Patient Population per NYHA Class

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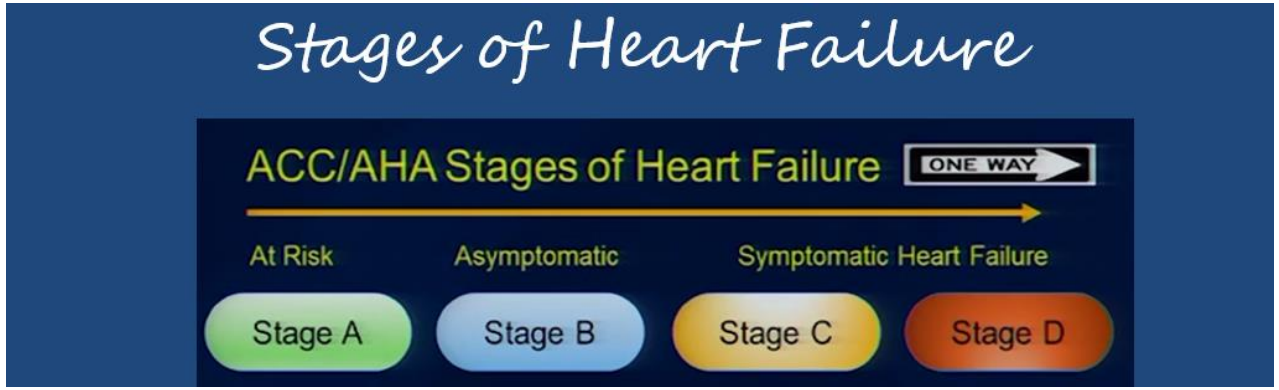
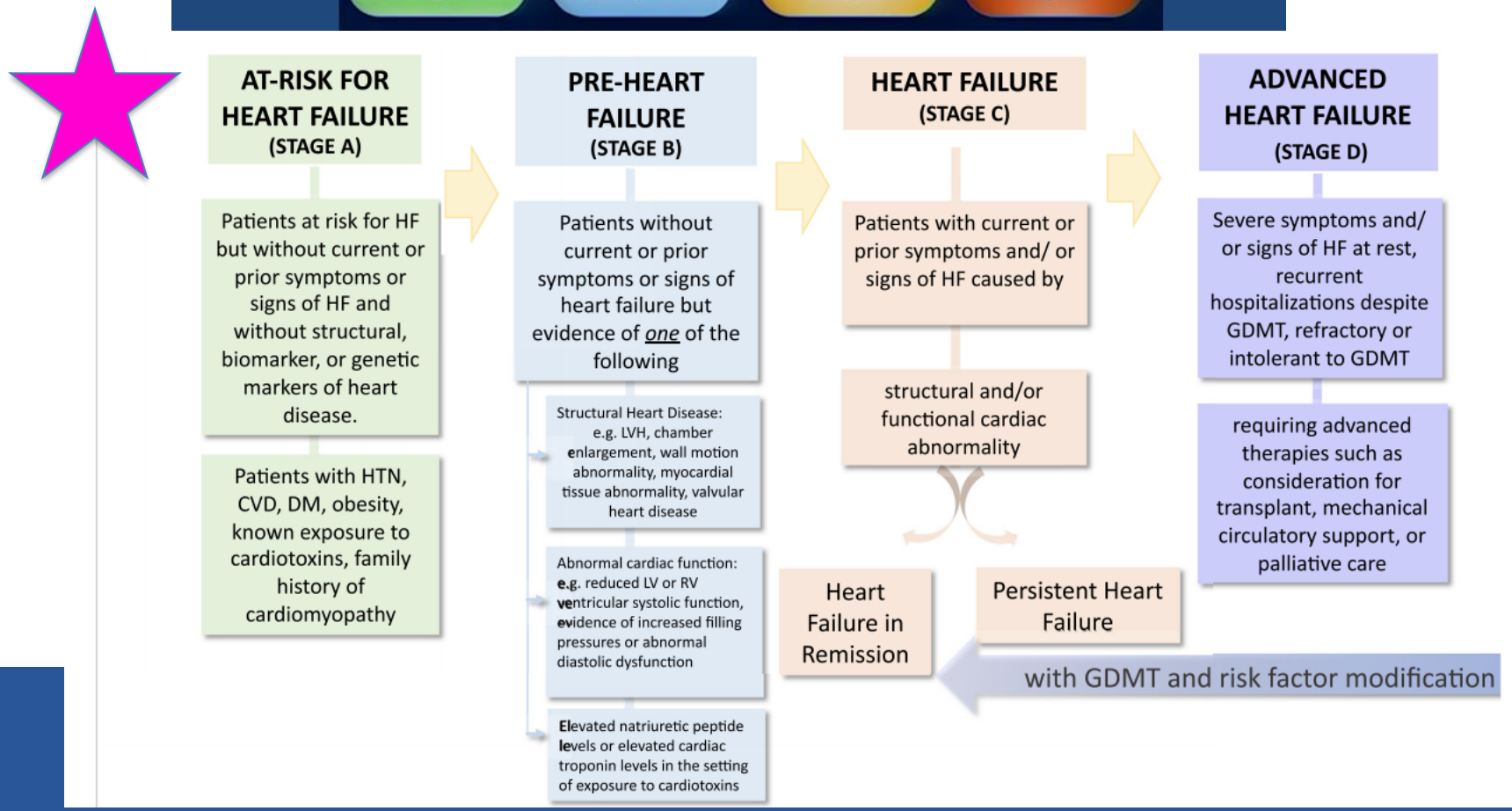
Stages in the Development and Progression of Heart Failure





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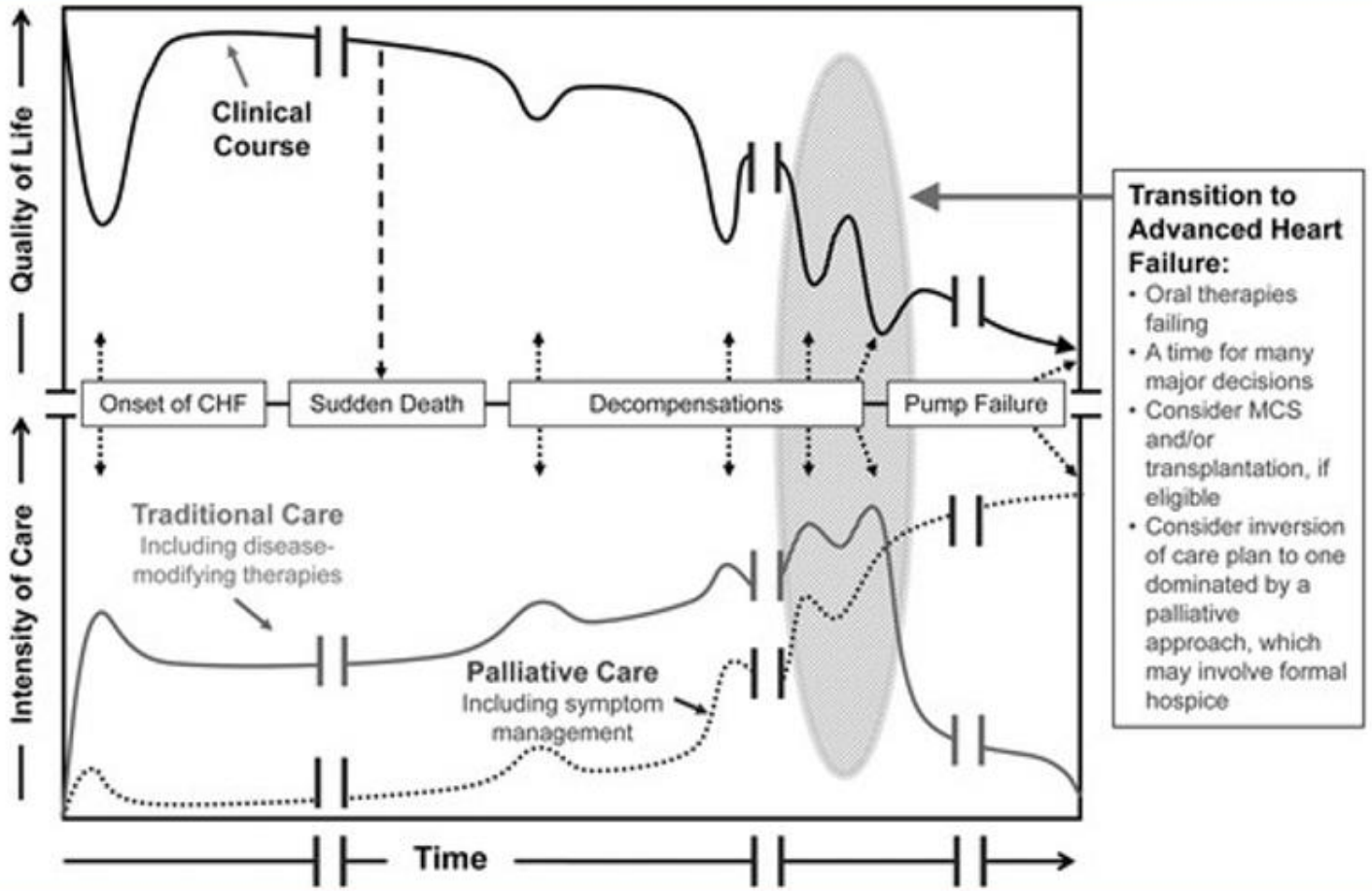
Transition to Advanced Heart Failure



Larry A. Allen. Circulation. Decision Making in Advanced Heart Failure, Volume: 125, Issue: 15, Pages: 1928-1952, DOI: (10.1161/CIR.0b013e31824f2173)

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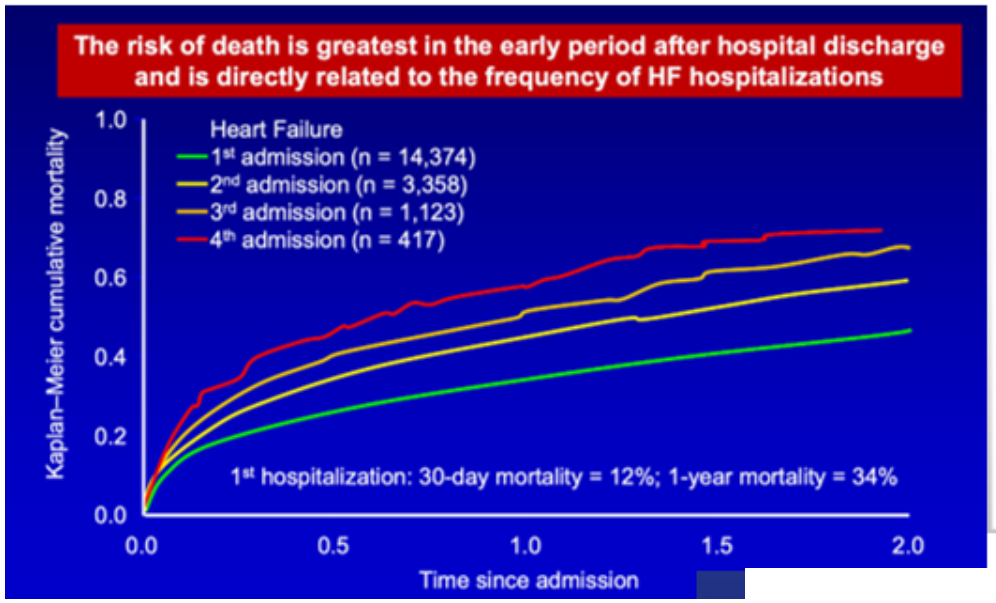
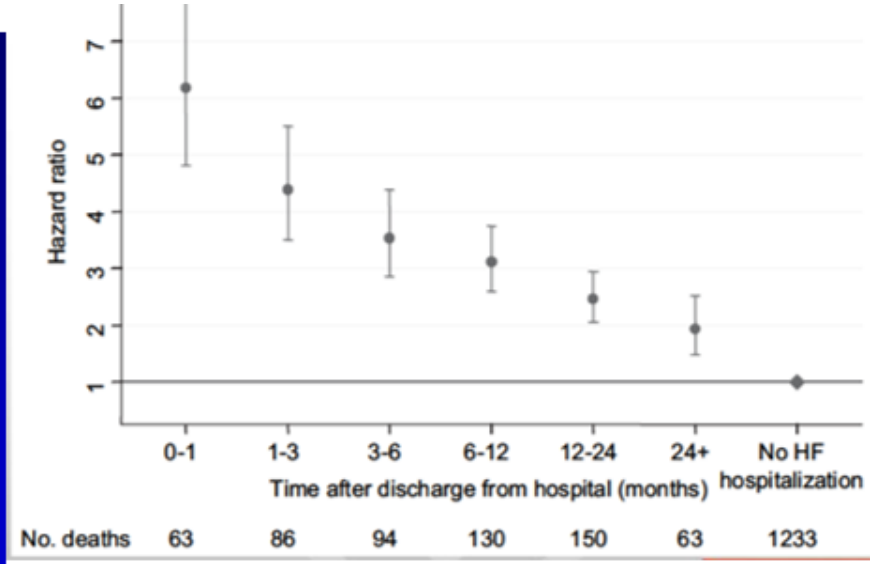
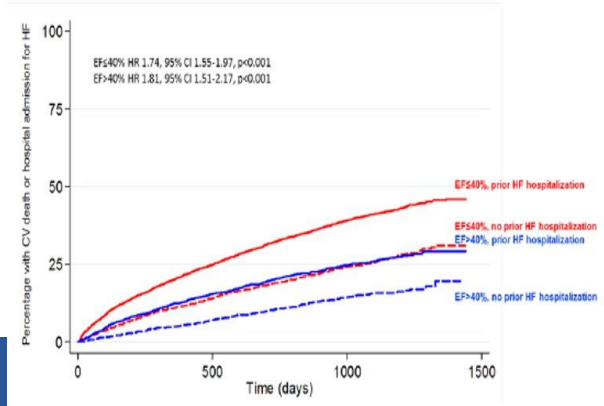
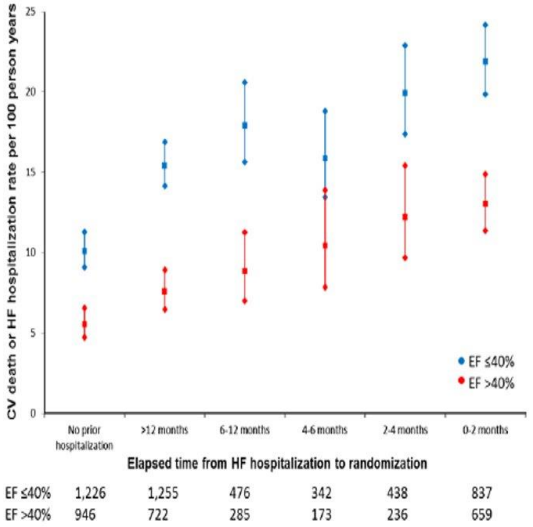
Acute Heart Failure Hospitalization:

1. ACM after Each Subsequent HF hospitalization
2. CV Death or HF hospitalization Likelihood after each hospitalization
3. recent prior HF hospitalization is associated with increased risk of clinical events in both reduced and preserved EF









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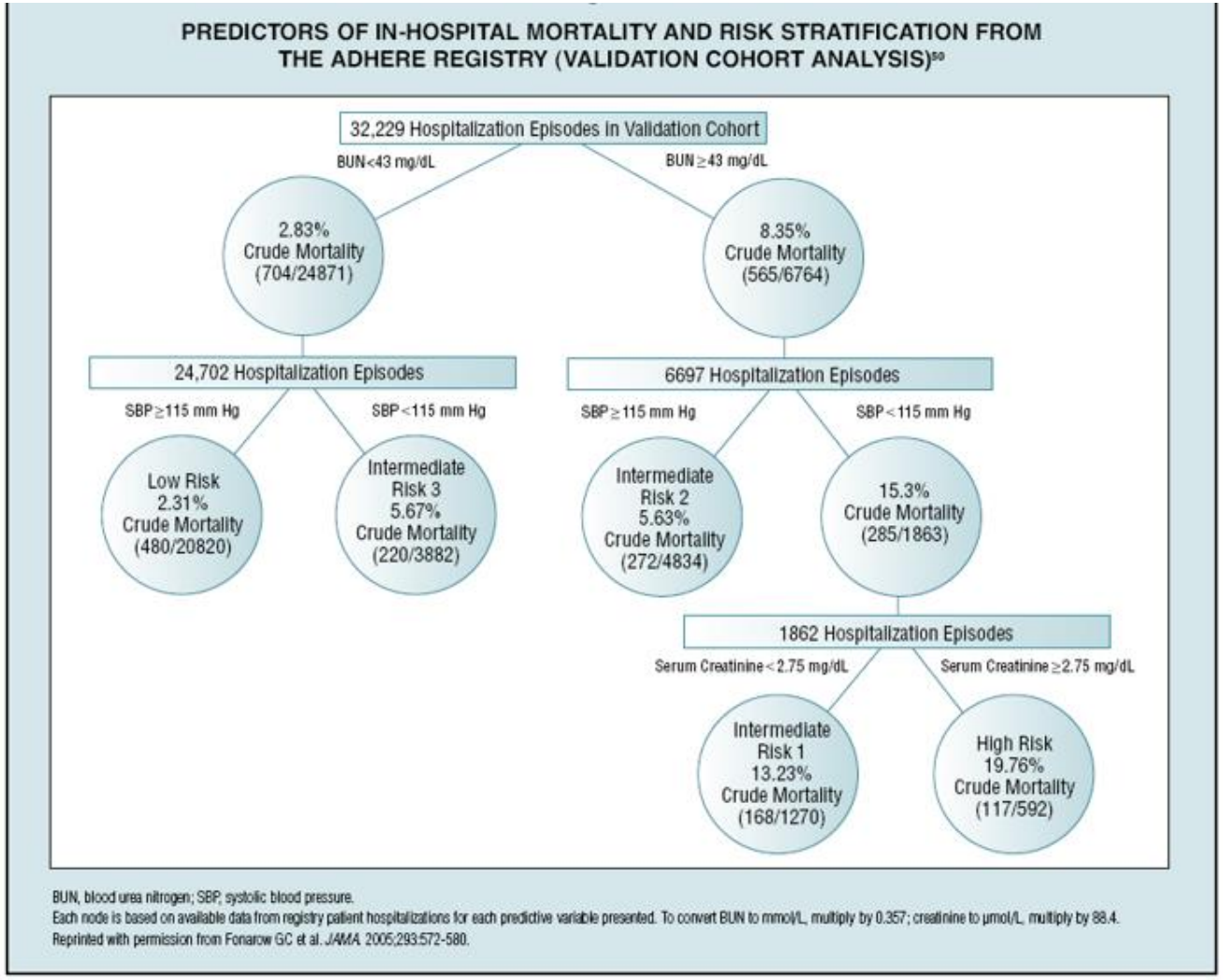
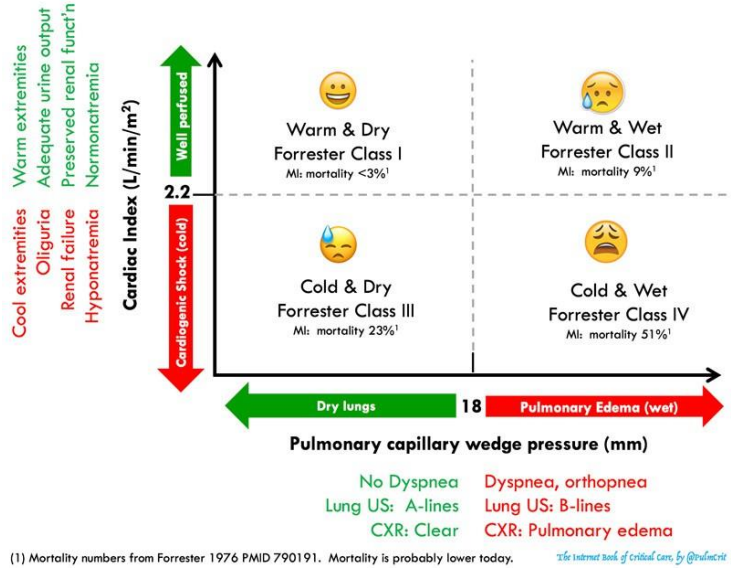
Acute Heart Failure:

- In-hospital
  - Length of stay (mean) 6.2 days
  - Mortality rate 4.1 —> 19.76%

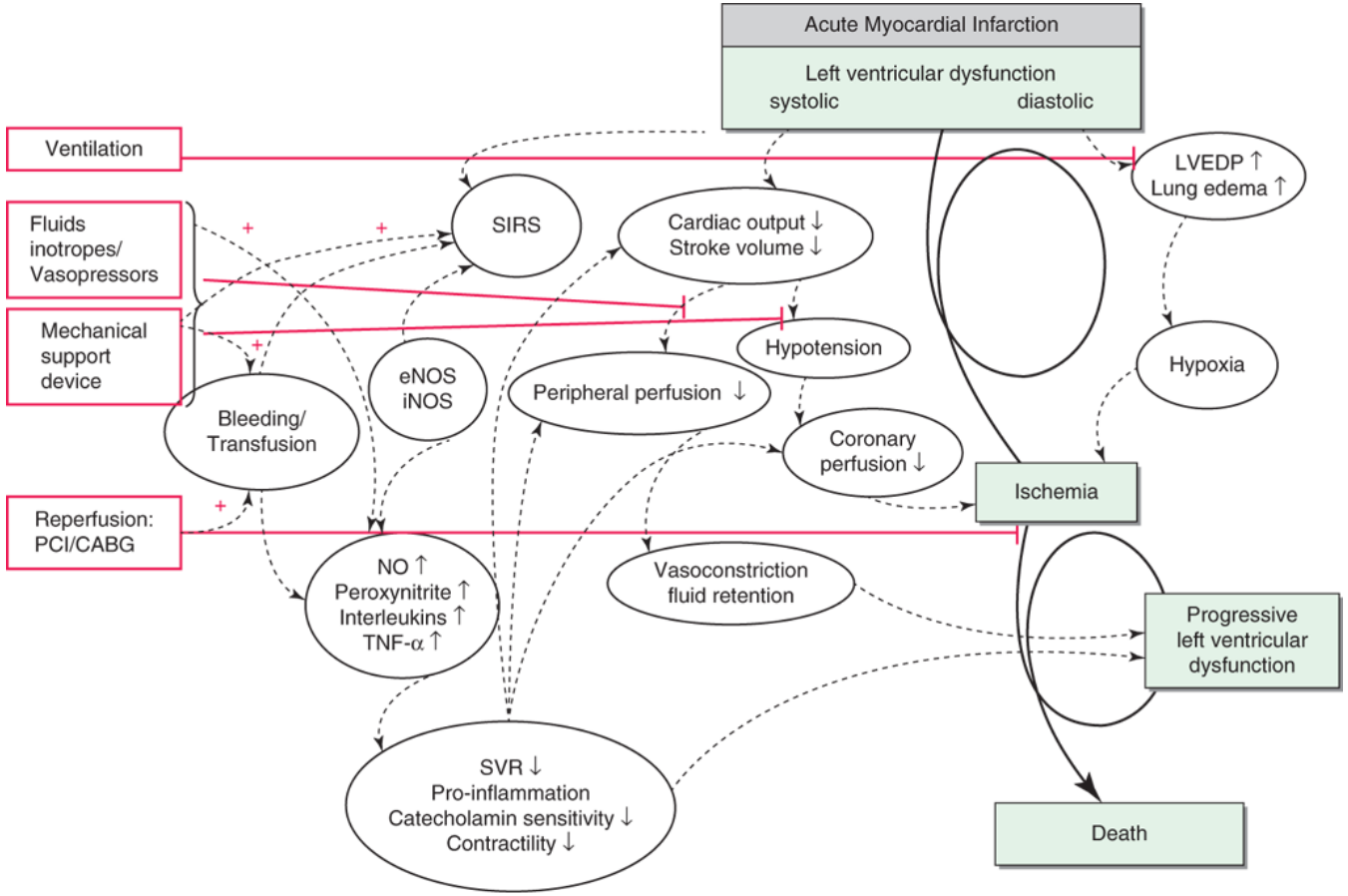
- Hospital readmissions
  - 20% at 30 days
  - 50% at 6 months





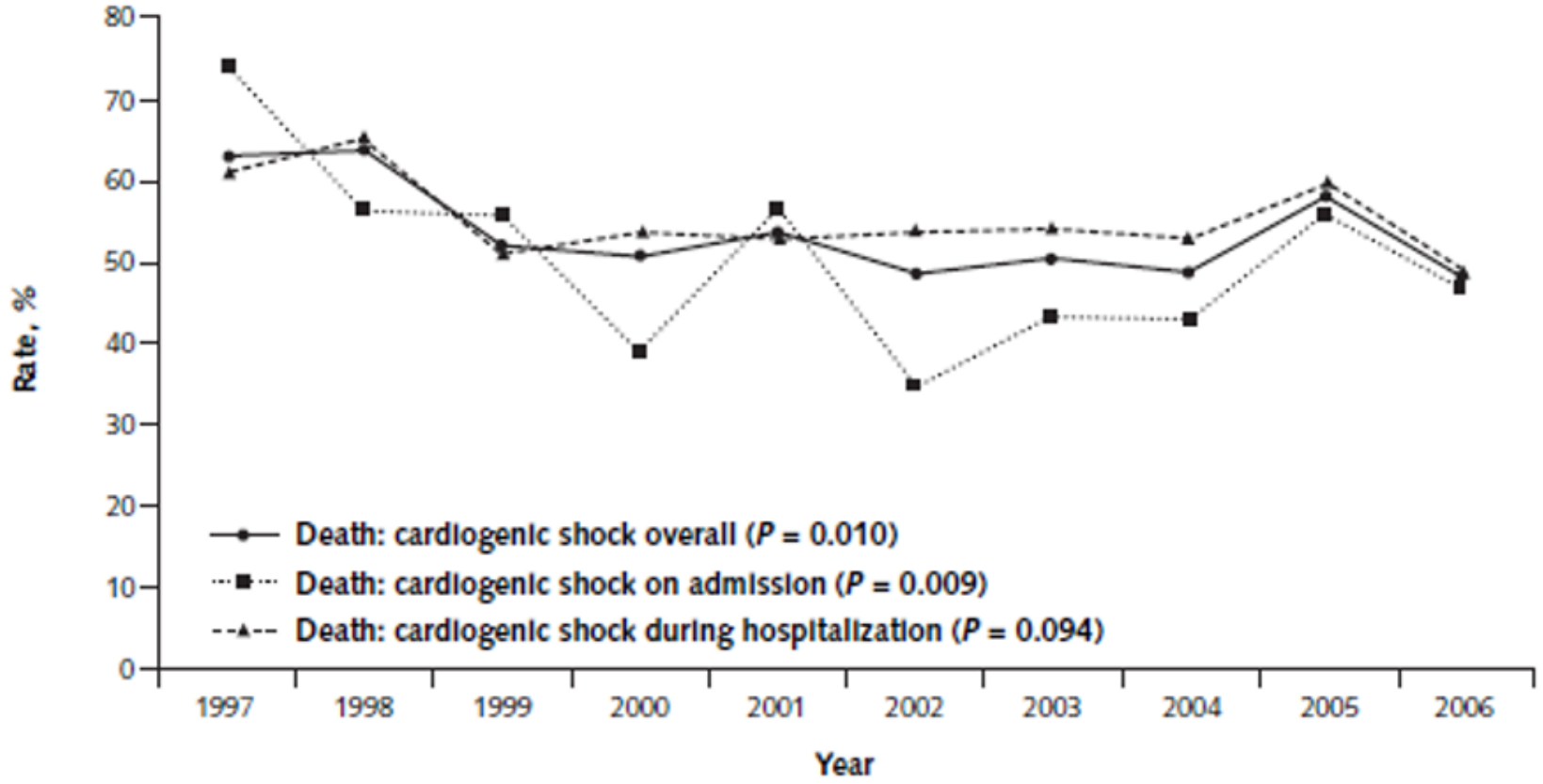
Van Diepen S, et al. *Circulation*. 2017;136:e232-e268.

		Volume Status	
		Wet	**Dry**
Peripheral Circulation	**Cold**	Classic Cardiogenic Shock (↓CI; ↑SVRI; ↑PCWP)	Euvolemic Cardiogenic Shock (↓CI; ↑SVRI; ↔PCWP)
	Warm	Vasodilatory Cardiogenic Shock or Mixed Shock (↓CI; ↓/↔SVRI; ↑PCWP)	Vasodilatory Shock (Not Cardiogenic Shock) (↑CI; ↓SVRI; ↓PCWP)

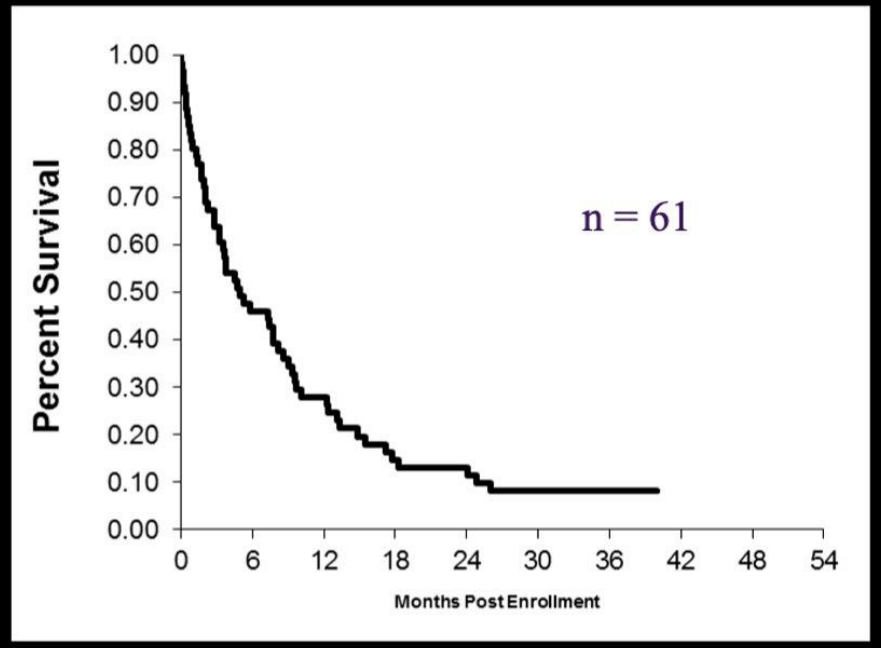


Pathophysiology of cardiogenic shock and potential treatment targets. The pathophysiological concept of the expanded cardiogenic shock spiral and treatment targets. CABG, coronary artery bypass grafting; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end diastolic pressure; NO, nitric oxide; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TNF, tumor necrosis factor. (Reproduced and adapted, with permission, from H Thiele et al: Shock in acute myocardial infarction: The Cape Horn for trials? Eur Heart J 31: 1828, 2010.)

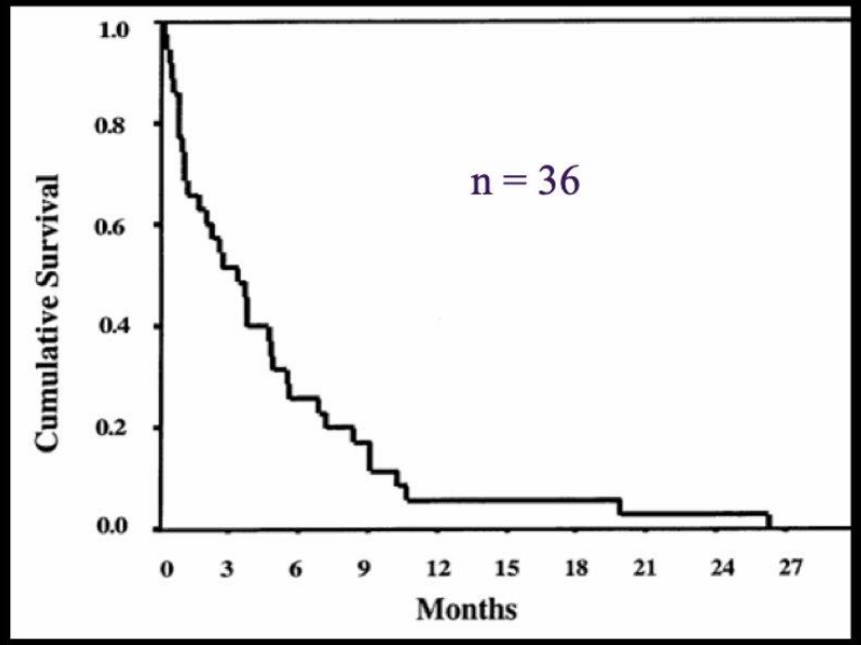
Cardiogenic Shock Survival…☹



Inotropic Therapy



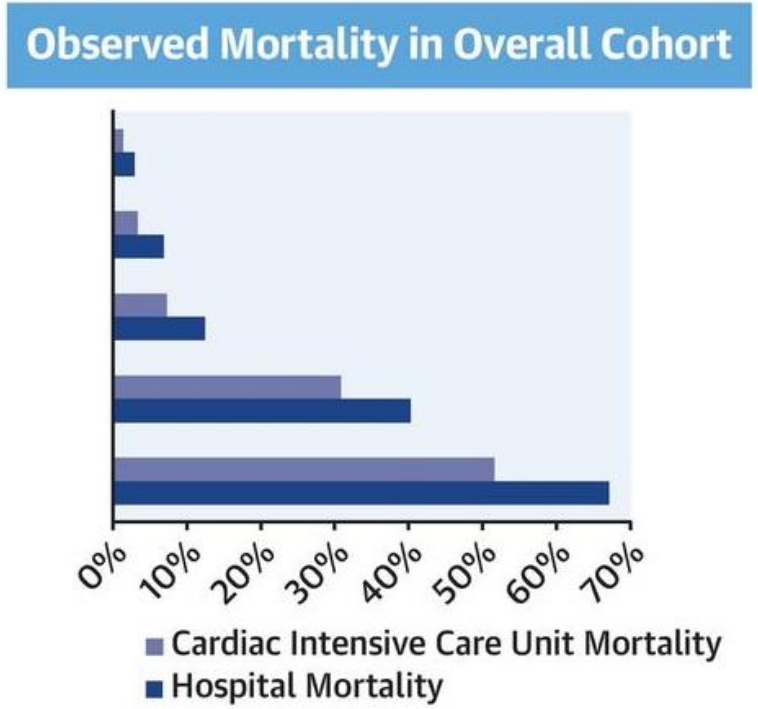
N Engl J Med 2001; 345:1435-43



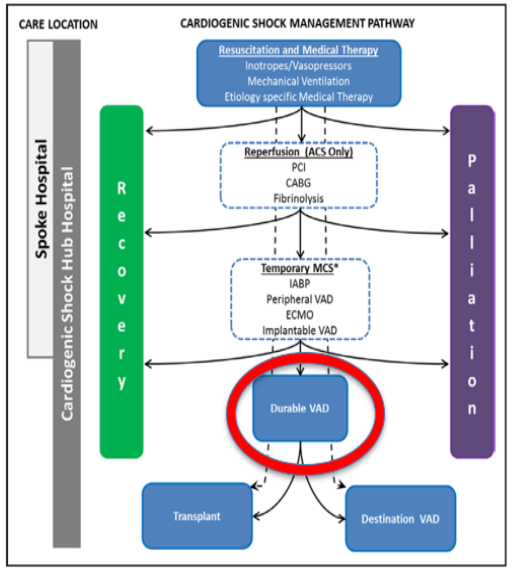
J Cardiac Failure 2003; 180 – 7

SCAI Shock Stages A through E…. Associated Cardiac Intensive Care Unit and Hospital Mortality in Each SCAI Shock Stage

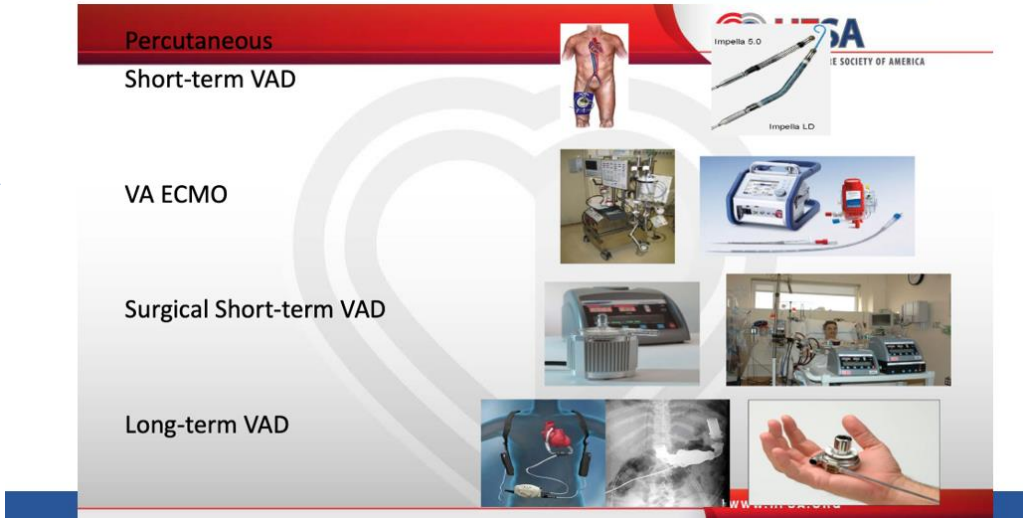
Cardiogenic Shock Stage	Study Definition
Stage A ("At risk")	Neither hypotension/tachycardia nor hypoperfusion
Stage B ("Beginning")	Hypotension/tachycardia WITHOUT hypoperfusion
Stage C ("Classic")	Hypoperfusion WITHOUT deterioration
Stage D ("Deteriorating)"	Hypoperfusion WITH deterioration NOT refractory shock
Stage E ("Extremis")	Hypoperfusion WITH deterioration AND refractory shock



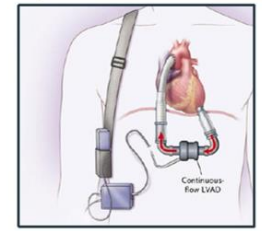
Potential Cardiogenic Shock Care Pathway, Care Location and Care Providers



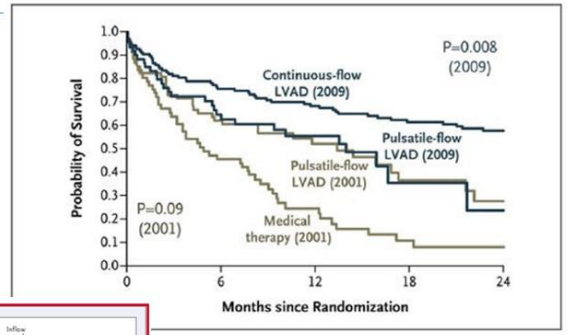
Acute Mechanical Circulatory Support Devices

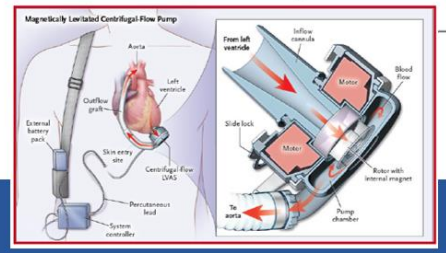


LVAD: Improve survival & QOL in Adv HF Refractory to Medical Therapy



HeartMate II: Continuous-flow LVAD





Fang JC. *N Engl J Med* 2009;361(23):2282-5

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New ACC/AHA/HFSA Guidelines

Yancy et al
2017 ACC/AHA/HFSA Heart Failure Focused Update

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

WRITING GROUP MEMBERS*

Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSA, *Chair*
Mariell Jessup, MD, FACC, FAHA, *Vice Chair*

Biykem Bozkurt, MD, PhD, FACC, FAHA*†
Javed Butler, MD, MBA, MPH, FACC, FAHA*‡
Donald E. Casey, Jr, MD, MPH, MBA, FACC§
Monica M. Colvin, MD, FAHA‖
Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSA‡
Gerasimos S. Filippatos, MD*
Gregg C. Fonarow, MD, FACC, FAHA, FHFSA*‡
Michael M. Givertz, MD, FACC, FHFSA*¶
Steven M. Hollenberg, MD, FACC#
JoAnn Lindenfeld, MD, FACC, FAHA, FHFSA*¶
Frederick A. Masoudi, MD, MSPH, FACC**
Patrick E. McBride, MD, MPH, FACC††
Pamela N. Peterson, MD, FACC, FAHA‡‡
Lynne Warner Stevenson, MD, FACC*‡
Cheryl Westlake, PhD, RN, ACNS-BC, FAHA, FHFSA¶

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EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

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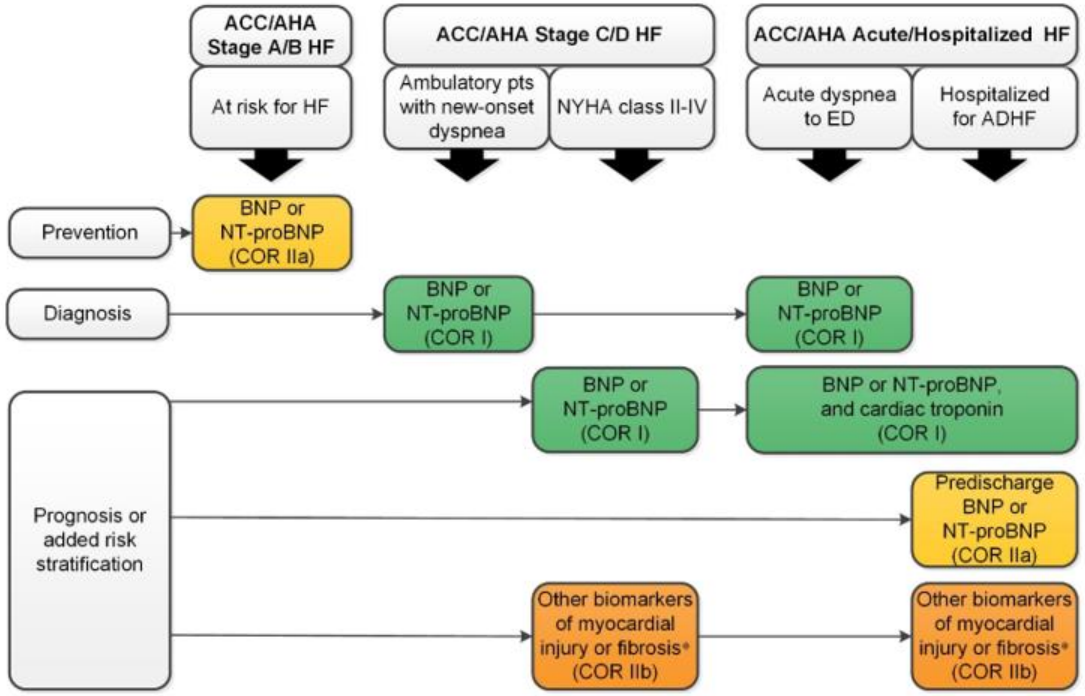
Biomarkers Indications for Use



*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin.
ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

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Biomarkers

Biomarkers Indications for Use

COR	LOE	Recommendation	Comment/ Rationale
IIa	B-R	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 left ventricular dysfunction (systolic or diastolic) or new-onset HF.	NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.

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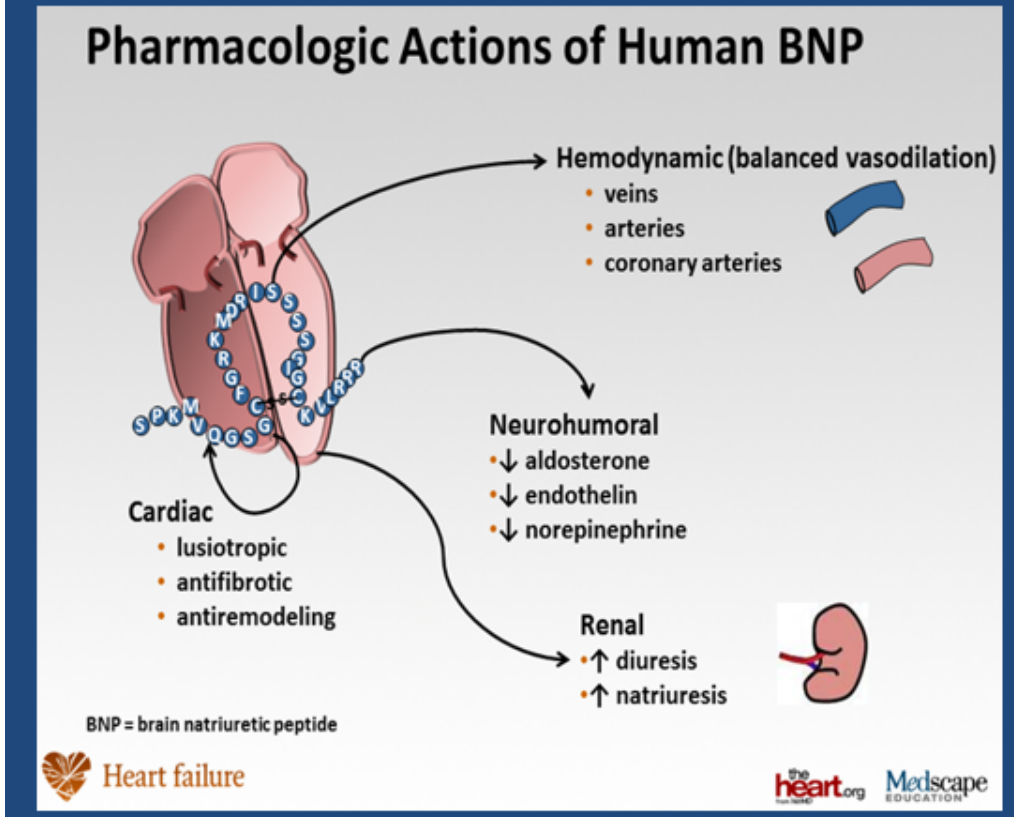
Biomarkers in Heart Failure
BNP (NT-proBNP) in Heart Failure



- Myocardial stress/strain/stretch → BNP
- Ventricles > atria
- BNP elevated in HF
  - Levels correlate with PCW and prognosis

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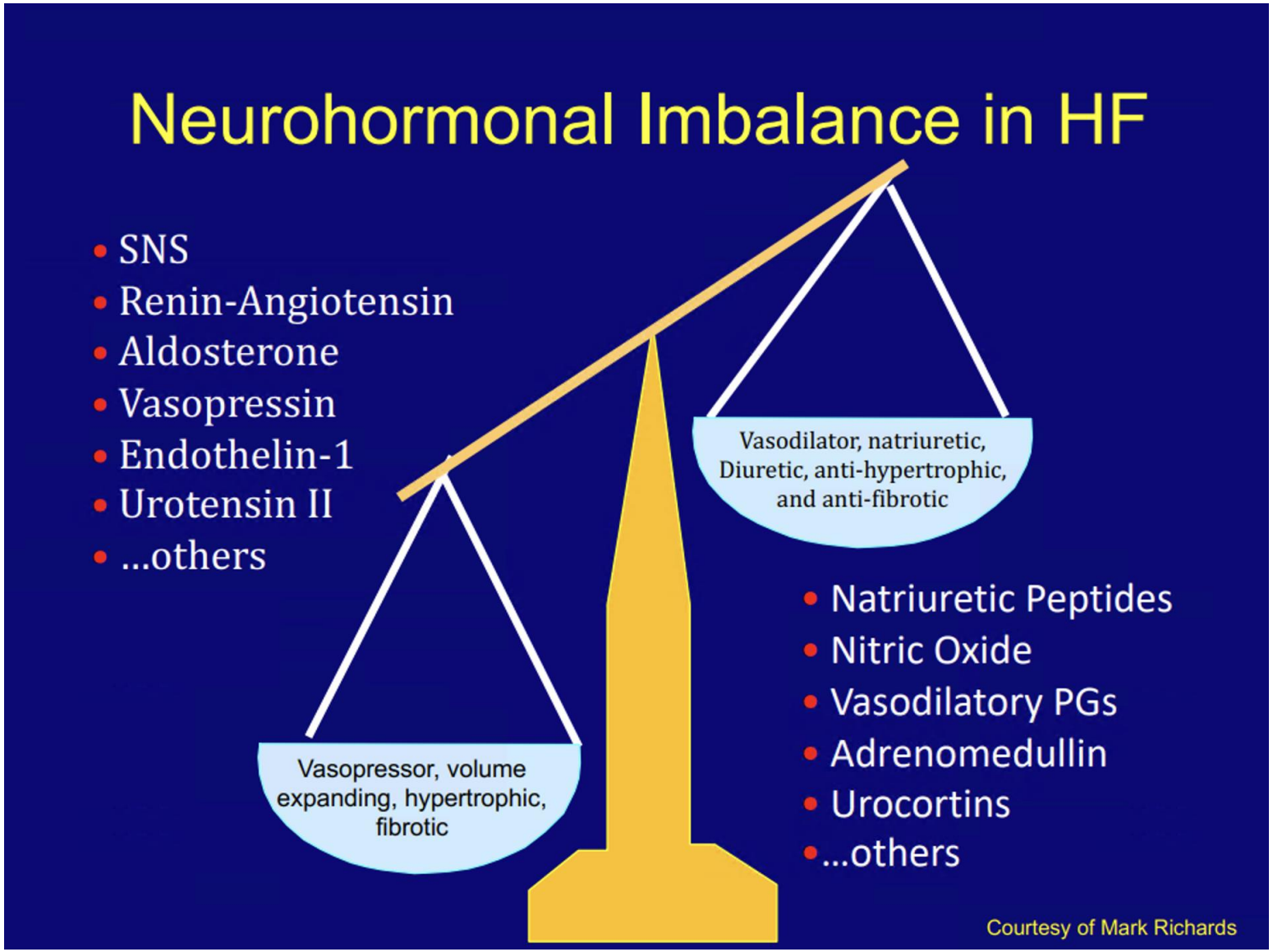
Neurohormonal Imbalance in HF



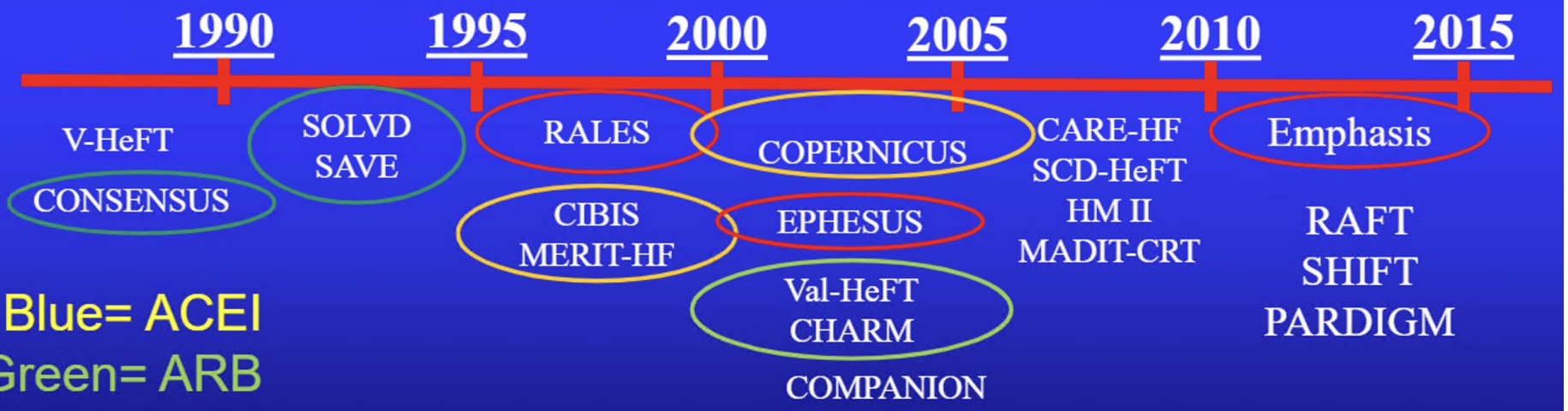
Important Pathophysiological Targets in Chronic, Hemodynamically Stable HFrEF (EF<=40%) and Treatments

Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACEIs/ARBs, aldosterone antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporter-2	SGLT2 inhibitors
Balanced vasodilation and oxidative stress modulation	HYD/ISDN
Elevated heart rate	Beta-blocker, ivabradine
Guanylyl cyclase	Soluble guanylyl cyclase stimulators
Relief of congestion	Diuretic agents
Ventricular arrhythmias	Implantable cardioverter-defibrillators
Ventricular dyssynchrony due to conduction abnormalities	Cardiac resynchronization therapy
Mitral regurgitation	Surgical or percutaneous mitral valve repair
Reduced aerobic capacity	Aerobic exercise training

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; HYD/ISDN = hydralazine/isosorbide dinitrate; SGLT2 = sodium-glucose cotransporter-2.

Evidence-Based HFrEF RCTs

All pharmacologic Therapies Have Focused on Neurohormonal Blockade



Blue= ACEI
Green= ARB
Red= MRA
Yellow=BB

Evidence-Based HFrEF Therapies

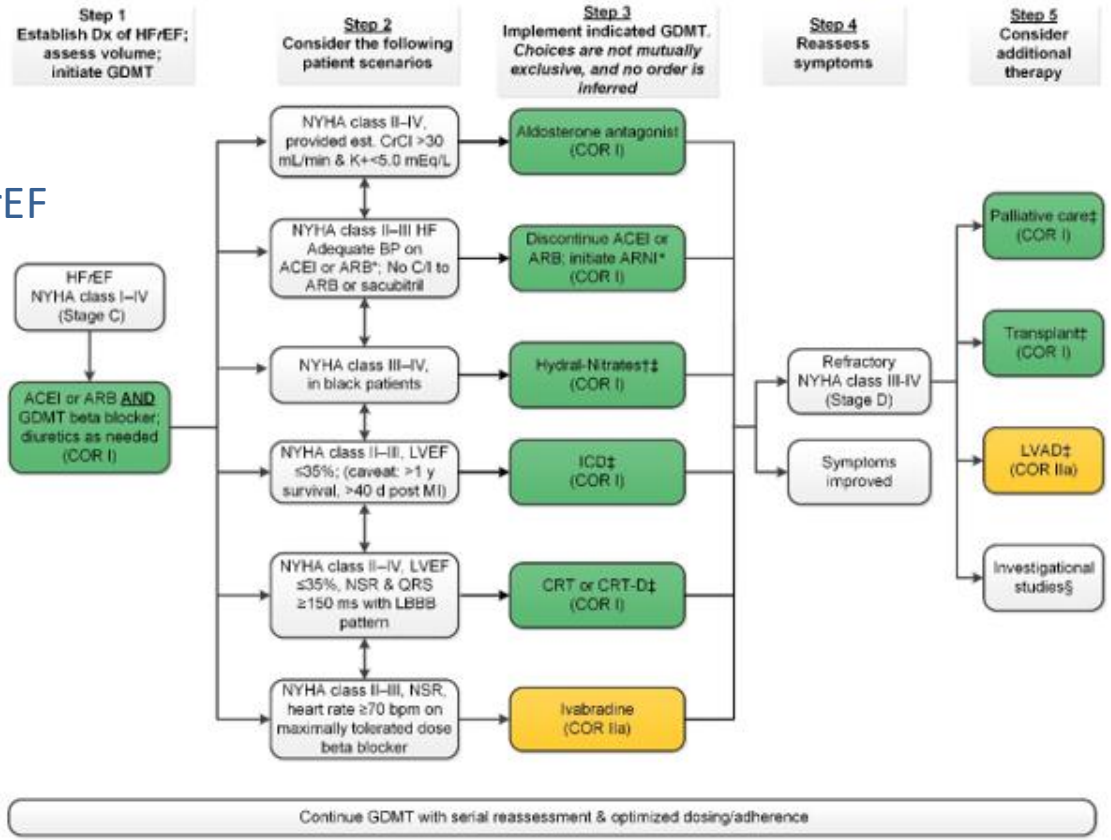
Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
ARNI	16%	36 over 27 months	27	21%
Beta-blocker	34%	28 over 12 months	9	41%
Aldosterone Antagonist	30%	9 over 24 months	6	35%
Hydralazine/Nitrate	43%	25 over 10 months	7	33%
CRT	36%	12 over 24 months	8	52%
ICD	23%	14 over 60 months	23	NA
Ivabradine	NA	NA	NA	26%

Updated from Fonarow GC, et al. *Am Heart J.* 2011;161:1024-1030.

Treatment of HFrEF Stage C and D

Pharmacologic Therapy for HFrEF (<=40%):

- ✓ ACEi, ARB, ARNI
- ✓ Beta Blockers
- ✓ MRAs
- ✓ Hydralazine/ISDN
- ✓ Ivabradine
- ✓ SGLT2i



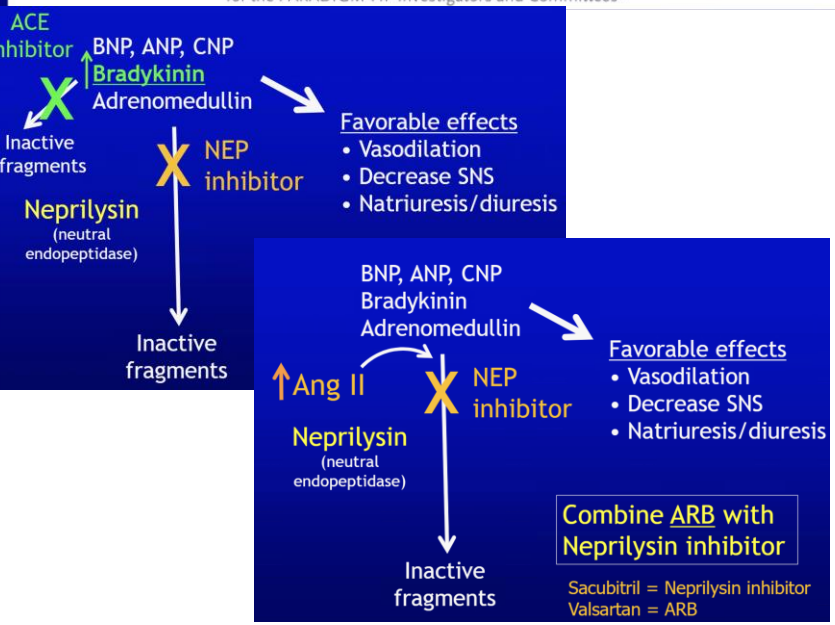
†Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.
‡See 2013 HF guideline.
§ Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy–device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

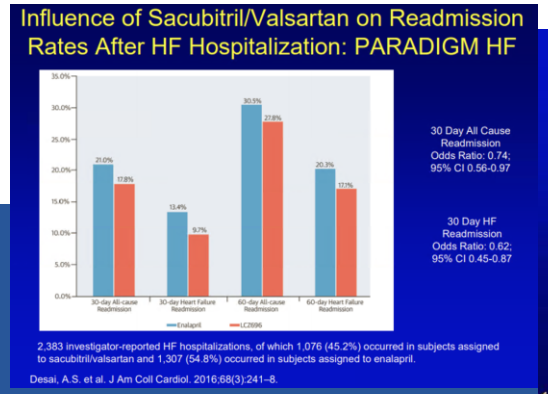
The NEW ENGLAND JOURNAL of MEDICINE

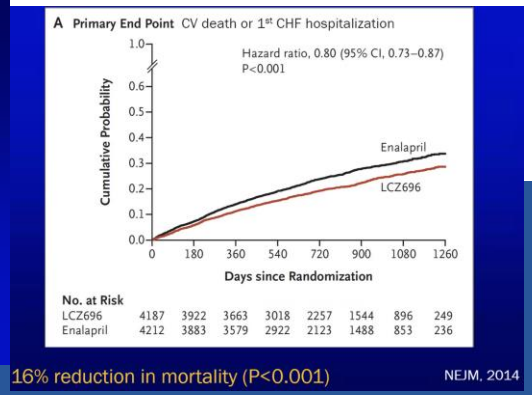
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*







Pharmacological Treatment for Stage C HF With Reduced EF

Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/ Rationale
I	ACE-I: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.	NEW: New clinical trial data prompted clarification and important updates.

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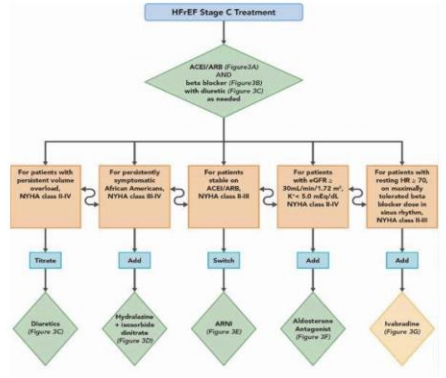
Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



Excerpted from:

Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction

December 2017
DOI: 10.1016/j.jacc.2017.11.025

AMERICAN COLLEGE of CARDIOLOGY

Pharmacological Treatment for Stage C HF With Reduced EF

Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/ Rationale
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.	NEW: New clinical trial data necessitated this recommendation.

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Pharmacological Treatment for Stage C HF With Reduced EF

Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/ Rationale
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.	NEW: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI.
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.	NEW: New clinical trial data.

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Health

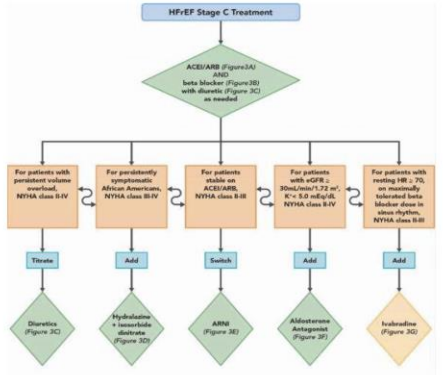
Pharmacological Treatment for Stage C HF With Reduced EF

Ivabradine

COR	LOE	Recommendations	Comment/ Rationale
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM*, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.	NEW: New clinical trial data.

*In other parts of the document, the term "GDMT" has been used to denote guideline-directed management and therapy. In this recommendation, however, the term "GDEM" has been used to denote this same concept in order to reflect the original wording of the recommendation that initially appeared in the "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure".

Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



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Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction

December 2017
DOI: 10.1016/j.jacc.2017.11.025

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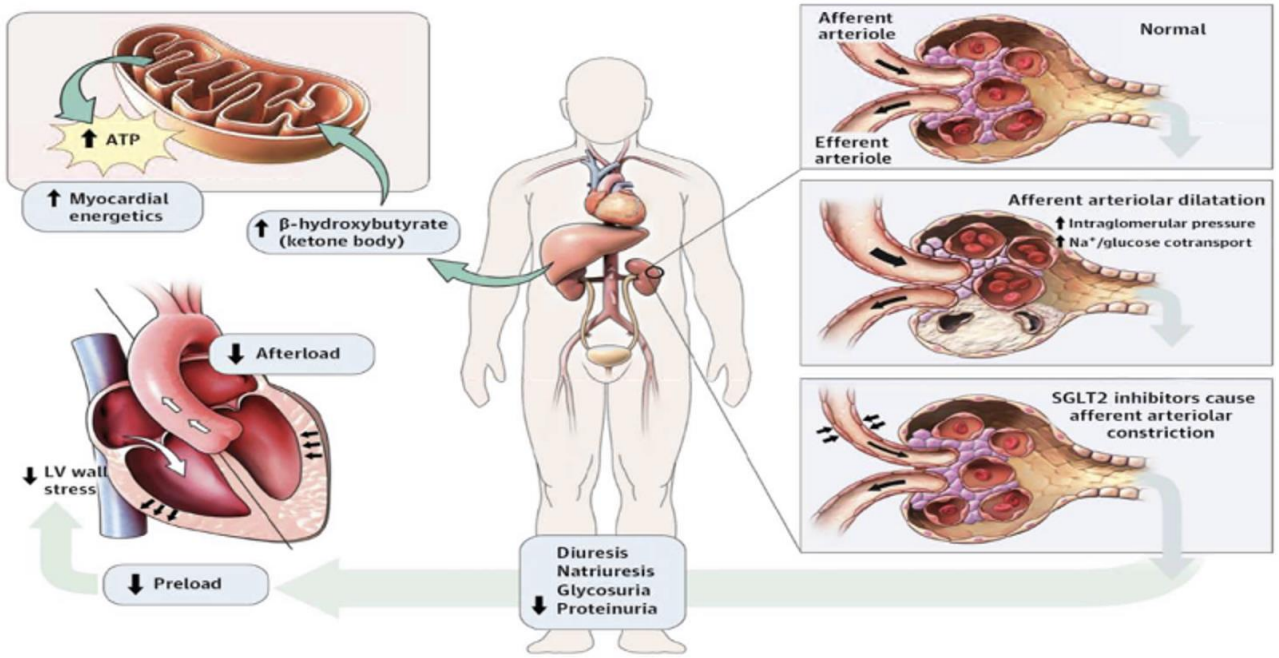
The Newest Therapy For Heart Failure with Reduced EF…SGLT2i (not in 2017 or 2021 consensus/updates)

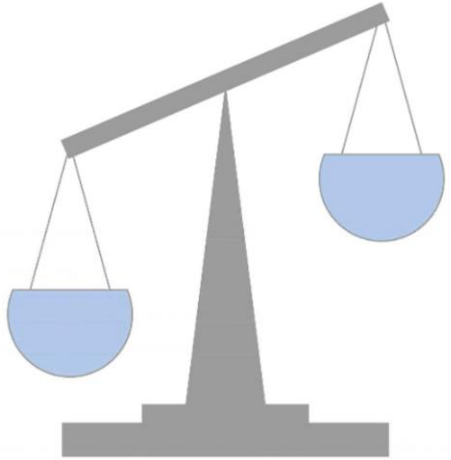
The JAMA Network

From: **The Metabolodiuretic Promise of Sodium-Dependent Glucose Cotransporter 2 InhibitionThe Search for the Sweet Spot in Heart Failure**

JAMA Cardiol. 2017;2(9):939-940. doi:10.1001/jamacardio.2017.1891



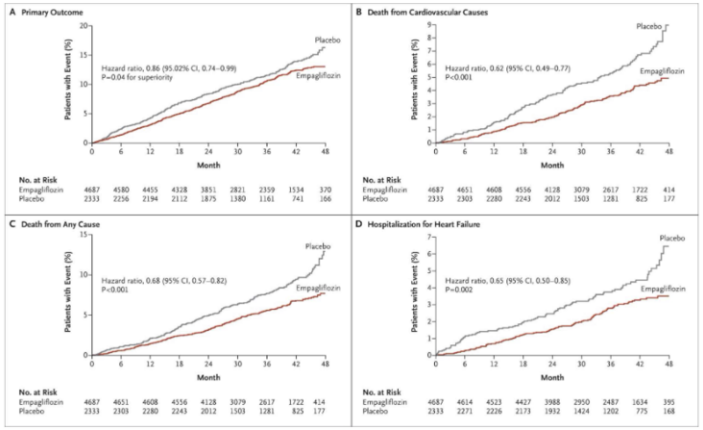
Favorable effects
Reduction of pre-load (diuretic effects)
Reduction of afterload (blood pressure, arterial stiffness)
Improvement of mitochondrial efficiency
Delay of decline in eGFR
Delay of micro- and macroalbuminuria
Weight loss
Reduction in epicardial adipose tissue
Improvement in glycemia
Reduction in uric acid



Unfavorable effects
Amputations (in particular toe, metatarsal)
Volume depletion/Hypotension
Diabetic ketoacidosis
Fractures
Urinary and genital infections

Figure Legend: Proposed Mechanism of Cardiorenal Protection With Sodium-Dependent Glucose Cotransporter 2 (SGLT2) InhibitorsAt the level of the kidney, SGLT2 inhibition promotes glycosuria and natriuresis. It also promotes afferent arterioral constriction resulting in a decrease in intraglomerular pressure. A reduction in preload and resultant left ventricular (LV) wall stress improves overall LV filling conditions. Additionally, metabolic effects of SGLT2 inhibition to improve myocardial energetics and reduce afterload have also been proposed as cardioprotective mechanisms. ATP indicates adenosine triphosphate.

Cardiovascular Outcomes and Death from Any Cause.



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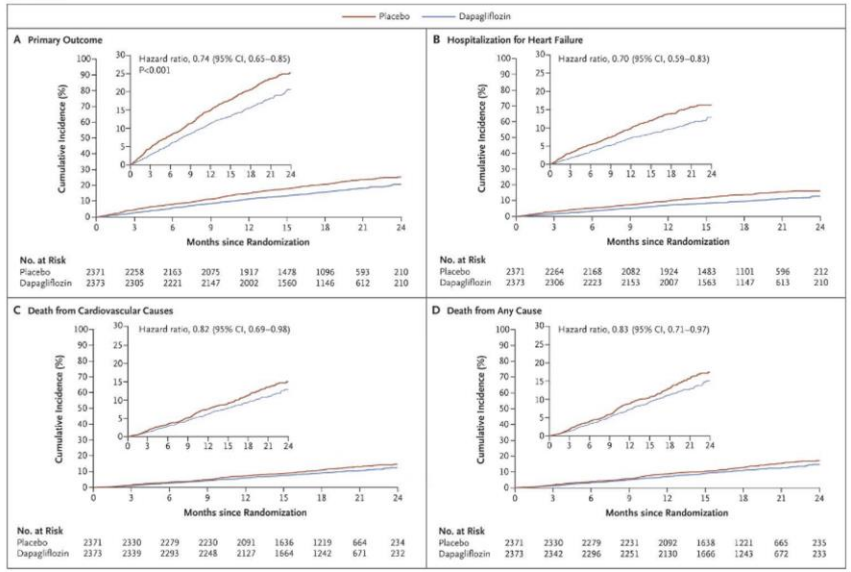
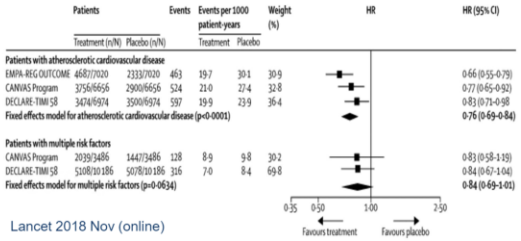


DAPA-HF: Effect of Dapagliflozin in Heart Failure, With or Without Diabetes

An inflection point in the care of patients with heart failure…

- Benefits seen in those with or without Diabetes
- Once a day therapy; single dose; no need for titration (N.B. low use of ARNI)
- No episodes of hypoglycemia or diabetic ketoacidosis
- Negligible incidence of amputations
- *NNT= 21; benefits seen even in those >75*

SGLT2 Inhibitors Reduce the Risk of Heart Failure Events in Type 2 Diabetes

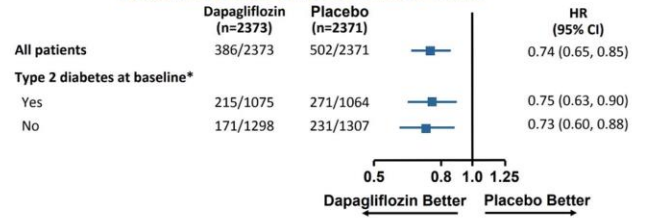


Lancet 2018 Nov (online)

DAPA-HF: Effect of Dapagliflozin in Heart Failure, With or Without Diabetes

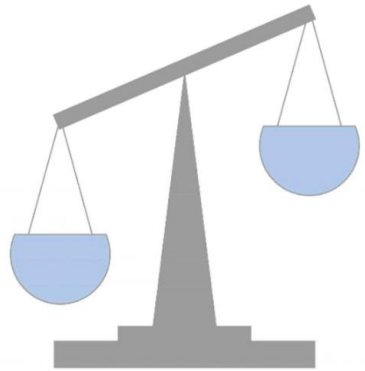
No diabetes/diabetes subgroup: Primary endpoint

Effect on Primary Endpoint of Cardiovascular Death and Serious Heart Failure Events



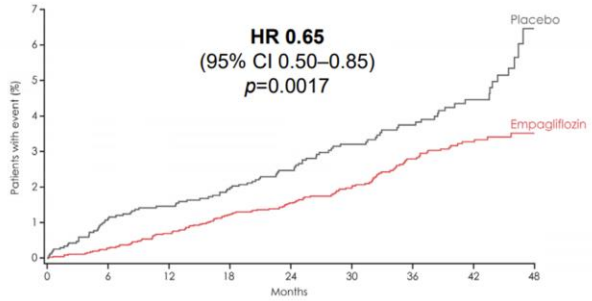
*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

Favorable effects
Reduction of pre-load (diuretic effects)
Reduction of afterload (blood pressure, arterial stiffness)
Improvement of mitochondrial efficiency
Delay of decline in eGFR
Delay of micro- and macroalbuminuria
Weight loss
Reduction in epicardial adipose tissue
Improvement in glycemia
Reduction in uric acid



Unfavorable effects
Amputations (in particular toe, metatarsal)
Volume depletion/Hypotension
Diabetic ketoacidosis
Fractures
Urinary and genital infections

EMPA-REG: Hospitalizations for Heart Failure



Zinman B et al. *N Engl J Med* 2015
Fitchett D et al. *Eur Heart J* 2016

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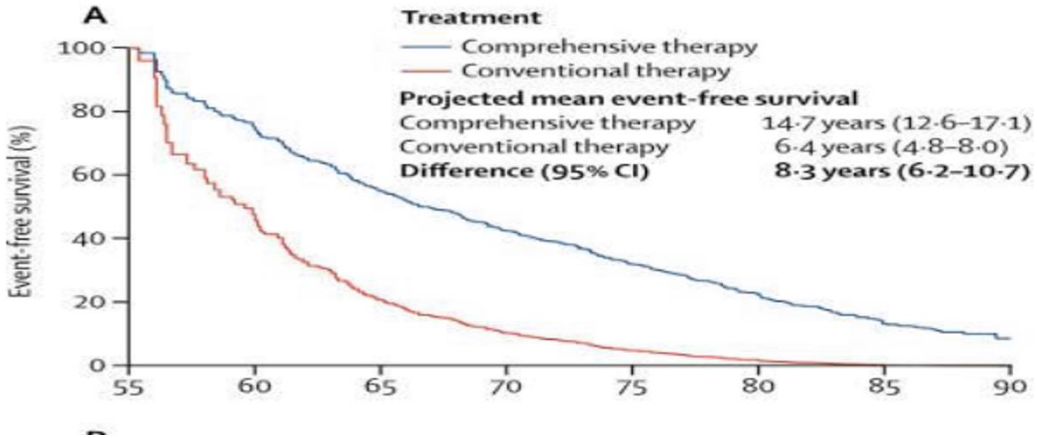
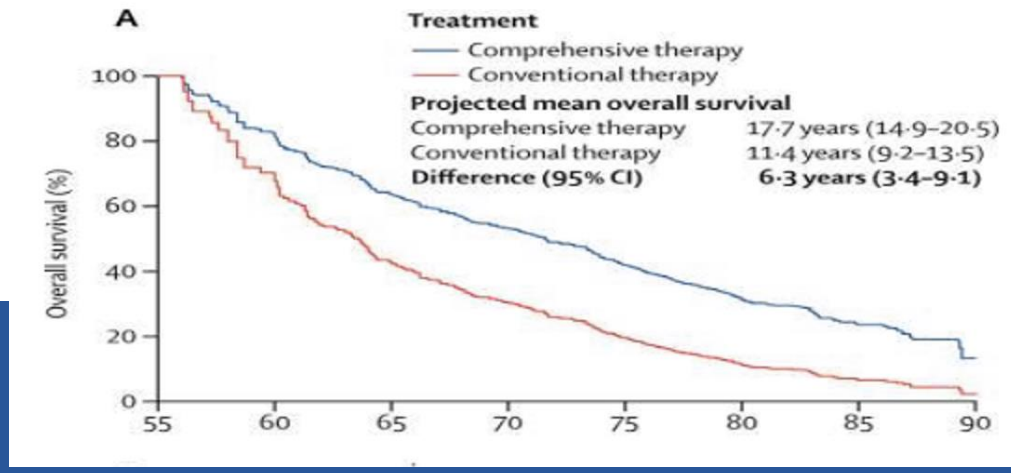
Event-free survival & Overall survival with comprehensive disease-modifying therapy vs conventional therapy (The Lancet 21 May 2020)





Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies

	Relative-risk	2 yr Mortality
None	- -	35%
ACEI or ARB	↓ 23%	27%
Beta Blocker	↓ 35%	18%
Aldosterone Ant	↓ 30%	13%
ARNI (replacing ACEI/ARB)	↓ 16%	10.9%
SGLT2 inhibitor	↓ 17%	9.1%

Cumulative risk reduction if all evidence-based medical therapies are used:
Relative risk reduction 74.0%, Absolute risk reduction: 25.9%, NNT = 3.9

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

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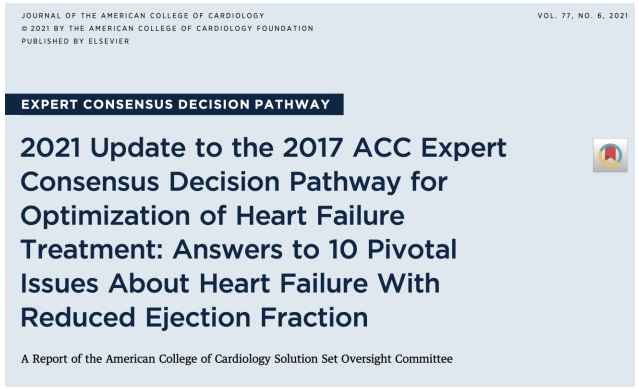

HEART FAILURE DEFINITIONS IN CONTEMPORARY CLINICAL PRACTICE GUIDELINES

ACCF/AHA (2013)[3]	HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue.
ESC (2016)[4]	
JCS/JHFS (2017)[5]	HF is 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.

GAPS IN CURRENT DEFINITIONS OF HEART FAILURE

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CURRENT… SELECTED CLASSIFICATION FRAMEWORKS USED FOR HEART FAILURE

Parameter	Explanation
NYHA functional class[3]	I, II, III, IV based on symptoms severity
EF[4]	HFrEF, HFmrEF, or HFpEF based on LVEF
Etiology[25]	Specific etiology of HF, for example, ischemic/nonischemic, valvular, hypertensive, infiltrative cardiomyopathy such as cardiac amyloidosis, peripartum cardiomyopathy, viral myocarditis chemotherapy-induced cardiomyopathy
Disease progression (ACCF/AHA)[3,54]	Stages A, B, C, or D according to presence of HF symptoms and signs and cardiac structural changes
MOGES[28]	Morphofunctional phenotype (M), organ (s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S)
INTERMACS Profiles for Advanced HF[108]	Profiles 1−7 according to symptoms, functional capacity, hemodynamic stability for patients who are considered for advanced HF therapies

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support[108]; MOGE(S) nosology system.[28]

CURRENT…SUMMARY OF DEFINITIONS OF Heart Failure (HF) INCLUSION CRITERIA IN RECENT CLINICAL TRIALS: HF WITH REDUCED (HFrEF) & PRESERVED (HFpEF) EJECTION FRACTION

HFrEF

Trial Name	Age, NYHA Functional Class	LVEF (%)	Natriuretic Peptides	HF Hospitalization or other
PARADIGM-HF [101]	Age ≥18 years NYHA II-IV	LVEF <35%	If previous hospitalization, BNP ≥100 pg/mL or NTproBNP ≥400 pg/mL If no previous hospitalization, BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL	Within previous 12 months
VICTORIA [104]	Age ≥18 years NYHA functional class II-IV	LVEF <45%	Within past 30 days: NSR, BNP >300 pg/mL, NT-proBNP >1,000 pg/mL AF BNP >500 pg/mL; NT-proBNP >1,600 pg/mL	Within 6 months or out-patient IV diuretics for HF within 3 months
DAPA-HF [66]	Age ≥18 years NYHA functional class II-IV	LVEF ≤40%	If HF hospitalization within 12 months: NT-proBNP ≥400 pg/mL If no hospitalization, NT-proBNP ≥600 pg/mL AF NT-proBNP ≥900 pg/mL	Diagnosis of HF for ≥2 months
EMPEROR-Reduced [65]	Age ≥18 years NYHA functional class II-IV	LVEF ≤40%	LVEF ≤30%, NT-proBNP ≥ 600pg/mL (NSR) or ≥ 1200pg/mL in AF LVEF 31%−35%, NT-proBNP ≥1000 pg/mL (NSR) or ≥2000 pg/mL in AF LVEF 36%−40%, NT-proBNP ≥2500 pg/mL (NSR) or ≥5000 pg/mL in AF LVEF <40% but HF hospitalization within 12 months, NT-proBNP ≥600 pg/mL (NSR) or ≥1200 pg/mL in AF	NYHA functional class II-IV ≥3 months
GALACTIC-HF [105]	Age ≥18 and <85 years, NYHA functional class II-IV	LVEF ≤35%	NT-proBNP ≥400pg/mL (NSR) or ≥1200 pg /mL in AF; or BNP ≥125 pg/mL (NSR) ≥375 pg/mL	Currently hospitalized for HF (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for HF within 12 months (outpatients) =

ACEI, angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, Angiotensin receptor-neprilysin inhibitor; CV, cardiovascular ; MRA, Mineralocorticoid receptor antagonist; NSR, Normal sinus rhythm.

HFpEF

Trial Name	Age, NYHA functional Class	LVEF (%)	Natriuretic Peptides	HF Hospitalization
TOPCAT [99]	Age ≥50 years NYHA functional class II-IV	LVEF ≥45%	BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL	Within previous 12 months, with management of HF a major component
PARAGON-HF [100]	Age≥50 years NYHA functional class II-IV	LVEF ≥45% and LAE LVH	If NSR, NT-proBNP >200 pg/mL If AF: >600 pg/mL Or if no previous hospitalization and If NSR: NT-proBNP >300 pg/mL, if AF: NT-proBNP >900 pg/mL	Within previous 9 months
EMPEROR-Preserved [106]	Age≥18 years NYHA functional class II-IV (≥3 months)	LVEF >40% (no prior history of LVEF ≤40%)	NT-proBNP >300 pg/mL in NSR or >900 pg/mL in AF	Within 12 months OR evidence of structural changes (LAE or increased LVM) on echo
DELIVER [107]	Age≥40 years NYHA functional class II-IV	(LVEF >40% and evidence of structural heart disease (ie, LAE or LVH)	Elevated natriuretic peptides	Medical history of HF ≥6 weeks before enrolment with at least intermittent need for diuretic treatment

AF, Atrial fibrillation; CV, cardiovascular; ECG, electrocardiogram; Echo, echocardiogram; LAE, left atrial enlargement; LBBB, Left bundle branch block; LVH, left ventricular hypertrophy; LVM, Left ventricular mass; NSR, Normal sinus rhythm.

UCI Health

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

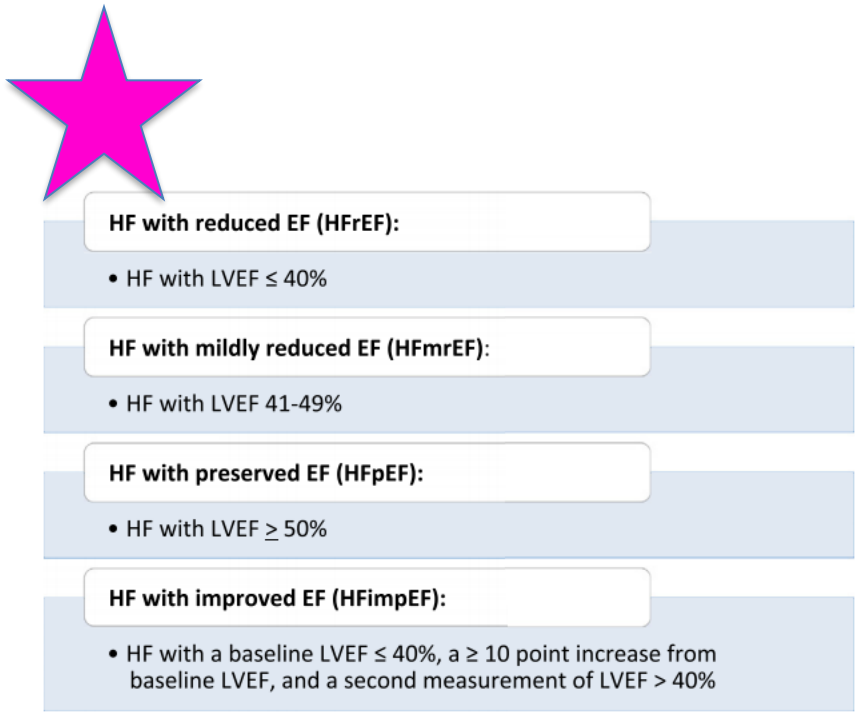
SUMMARY OF KEY POINTS

In this document, we propose a universal definition of heart failure (HF) as the following: HF is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion. We propose revised stages of HF as follows. At-risk for HF (Stage A), for patients at risk for HF but without current or prior symptoms or signs of HF and without structural or biomarkers evidence of heart disease. Pre-HF (stage B), for patients without current or prior symptoms or signs of HF, but evidence of structural heart disease or abnormal cardiac function, or elevated natriuretic peptide levels. HF (Stage C), for patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality. Advanced HF (Stage D), for patients with severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite guideline-directed management and therapy (GDMT), refractory or intolerant to GDMT, requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care. Finally, we propose a new and revised classification of HF according to left ventricular ejection fraction (LVEF). The classification includes HF with reduced EF (HFrEF): HF with an LVEF of ≤40%; HF with mildly reduced EF (HFmrEF): HF with an LVEF of 41% to 49%; HF with preserved EF (HFpEF): HF with an LVEF of ≥50%; and HF with improved EF (HFimpEF): HF with a baseline LVEF of ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF of >40%. (*J Cardiac Fail 2021;27:387–413*)

Proposed New Classifications of Heart Failure According to Ejection Fraction

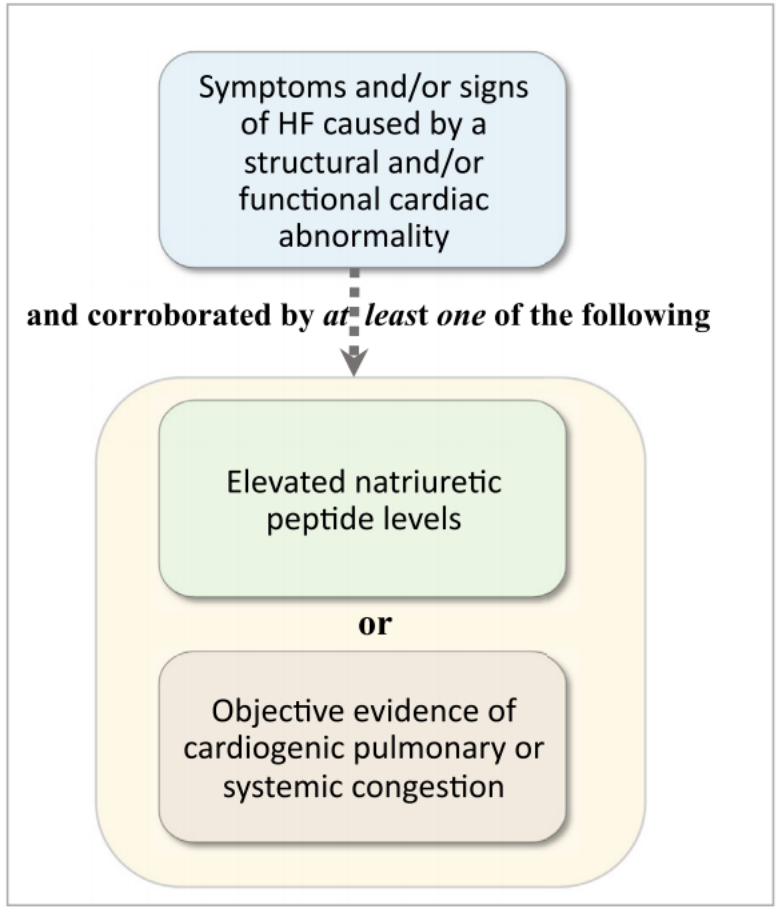
- ✓ LVEF defines a group known to respond to life-prolonging therapy from RCTs
- ✓ LVEF provides prognostic information
  - ✓ NOTE:
    - ✓ LVEF is not a singular measurement where LV function is assessed in isolation
      - ✓ LV chamber volumes and other cardiac structural & functional parameters are important (HFpEF w/LV dilatation)
- ✓ Recognize the need to identify effective treatment strategies in HFmrEF, HFpEF and HFimpEF:
  - ✓ Growing body of evidence that GDMT for various EF's may apply to other ranges and result in reverse remodeling and improvement in the LVEF

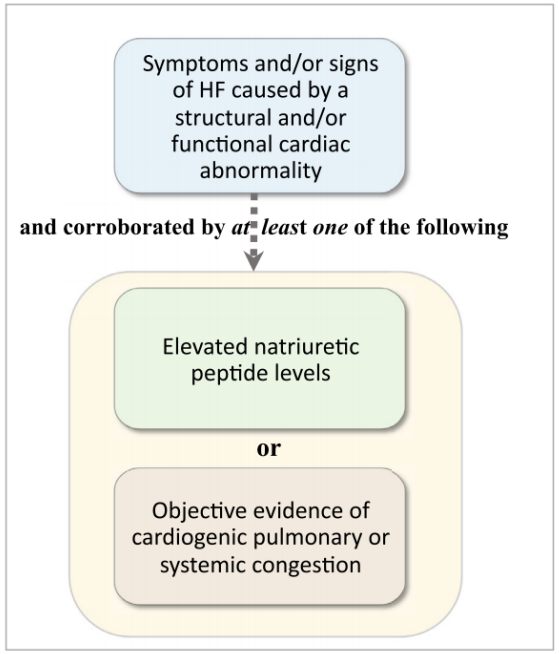
HF is heterogenous



✓UNIVERSAL DEFINITION OF HEART FAILURE:

1. SIMPLE BUT COMPREHENSIVE
2. NEAR UNIVERSAL APPLICABILITY
3. PROGNOSTIC AND THERAPEUTIC VALIDITY
4. ACCEPTABLE SENSITIVITY AND SPECIFITY





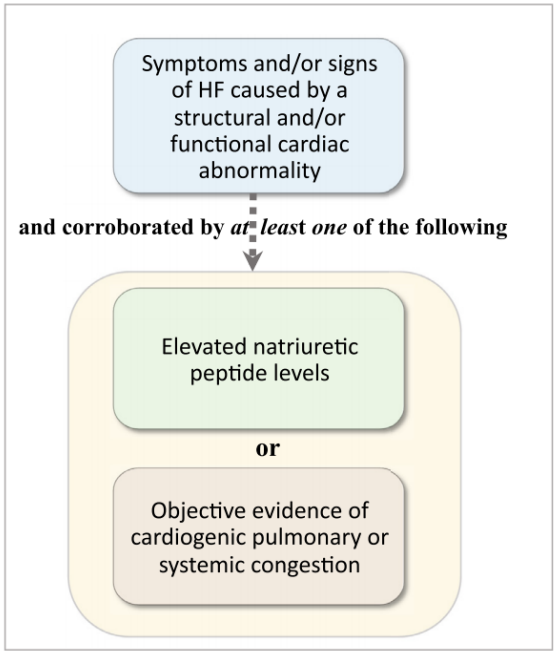
HF is a syndrome with…

- current or prior symptoms of HF and/or
- signs caused by a structural and/or functional cardiac abnormality as determined by →
  - EF of < 50%
  - abnormal cardiac chamber enlargement
  - E/E' of > 25
  - moderate/severe ventricular hypertrophy
  - moderate/severe valvular obstructive or regurgitant lesions

Symptoms of HF
Typical
Breathlessness
Orthopnea*
Paroxysmal nocturnal dyspnea*
Reduced exercise tolerance*
Fatigue, tiredness†
Ankle swelling*
Inability to exercise*
Swelling of parts of the body other than ankles
Bendopnea
Less typical
Nocturnal cough
Wheezing
Bloated feeling‡
Postprandial satiety‡
Loss of appetite
Decline in cognitive function, confusion (especially in the elderly)†
Depression
Dizziness, syncope†
Signs of HF
More specific
Elevated jugular venous pressure*
Third heart sound*
Summation gallop with third and fourth heart sounds
Cardiomegaly, laterally displaced apical impulse
Hepatojugular reflux
Cheyne Stokes respiration in advanced HF†
Less specific
Peripheral edema (ankle, sacral, scrotal)
Pulmonary rales*
Unintentional weight gain (>2 kg/week)
Weight loss (in advanced HF) with muscle wasting and cachexia
Cardiac murmur
Reduced air entry and dullness to percussion at lung bases suggestive of pleural effusion
Tachycardia, irregular pulse
Tachypnea
Hepatomegaly/ascites
Cold extremities†
Oliguria
Narrow pulse pressure

*Commonly used in clinical trials, registries, risk scoring, and have been tested for sensitivity and specificity.
†Common in low perfusion, low cardiac output states.
‡Can be typical in the setting of right HF or biventricular failure.

Universal Definition of Heart Failure, continued….



Signs & symptoms corroborated by at least one of the following:

- Elevated natriuretic peptide levels

OR

- Objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities (rest or exercise):
  - Imaging: CXR, Echo w/evidence of elevated filling pressures
  - Hemodynamics: right heart catheterization/PAC

Table 8. Natriuretic Peptide Levels Supporting Definition of HF

	Ambulatory	Hospitalized/ Decompensated
BNP, pg/mL	≥35	≥ 100
NT-proBNP, pg/mL	≥ 125	≥ 300

Table 9. Causes of Elevated Natriuretic Peptide Levels Other than Primary Diagnosis of HF

Cardiovascular causes
Acute coronary syndrome, MI
Pulmonary embolism
Myocarditis
Hypertrophic cardiomyopathy
Valvular heart disease
Congenital heart disease
Atrial or ventricular arrhythmias
Heart contusion, cardiac infiltration or malignancy
Cardioversion, ICD shock
Pericardial disease
Invasive or surgical procedures involving the heart
Pulmonary hypertension, right ventricular failure
Infiltrative cardiomyopathies
Noncardiovascular causes
Advanced age
Kidney disease
Critical illnesses including Sepsis syndrome, cytokine syndrome
Ischemic or hemorrhagic stroke
Pulmonary disease (pneumonia, chronic obstructive pulmonary disease)
Liver disease
Severe anemia
Severe metabolic and hormone abnormalities (eg, thyrotoxicosis, diabetic ketoacidosis, severe burns)
Causes of lower natriuretic peptide levels
Obesity or increased BMI
Pericardial disease*

*In certain patients with pericardial disease and effusion, natriuretic peptides may be lower and increase after pericardiocentesis.

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2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Trea
Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction
A Report of the American College of Cardiology Task Force on Expert Consensus Decis
Pathways

Clyde W. Yancy, James L. Januzzi Jr., Larry A. Allen, Javed Butler, Leslie L. Davis, Gregg C. Fonarow, Nasrien E. Ibrahim, Mariell Jessup, JoAnn Lindenfeld, Thomas M. Maddox, Frederick A. Masoudi, Shweta R. Motiwala, J. H Patterson, Mary Norine Walsh and Alan Wasserman

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EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

FIGURE 1 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

2017 ACCF/AHA Heart Failure Guidelines

How to implement GDMT...

Issue 1. Initiate, Add, or Switch
Treatment algorithm for GDMT including novel therapies (*Figures 2* and *3*)

Issue 2. Titration
Target doses, indications, contraindications, and other considerations of select GDMT for HFrEF (*Tables 1, 2, 3, 4, 5*)

Considerations for monitoring

How to address challenges with...

Issue 3. Referral
Triggers for referral to HF specialist (*Table 6*)

Issue 4. Care Coordination
Essential skills for an HF team (*Table 7*)

Infrastructure for team-based HF care (*Table 8*)

Issue 5. Adherence
Causes of nonadherence *(Table 9)*

Considerations to improve adherence *(Table 10)*

Issue 6. Specific Patient Cohorts
Evidence-based recommendations and assessment of risk for special cohorts:
African Americans, older adults, and the frail (*Table 11*)

Issue 7. Medication Cost and Access
Strategies to reduce patients' cost of care (*Table 12*)
Helpful information for completion of prior authorization forms (*Table 13* and *Supplemental Appendix 2)*

How to manage...

Issue 8. Increasing Complexity
Twelve pathophysiological targets in HFrEF and treatments (*Table 14*)

Ten principles and actions to guide optimal therapy

Issue 9. Comorbidities
Common cardiovascular and noncardiovascular comorbidities with suggested actions (*Table 15*)

Issue 10. Palliative/ Hospice Care
Seven principles and actions to consider regarding palliative care

GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

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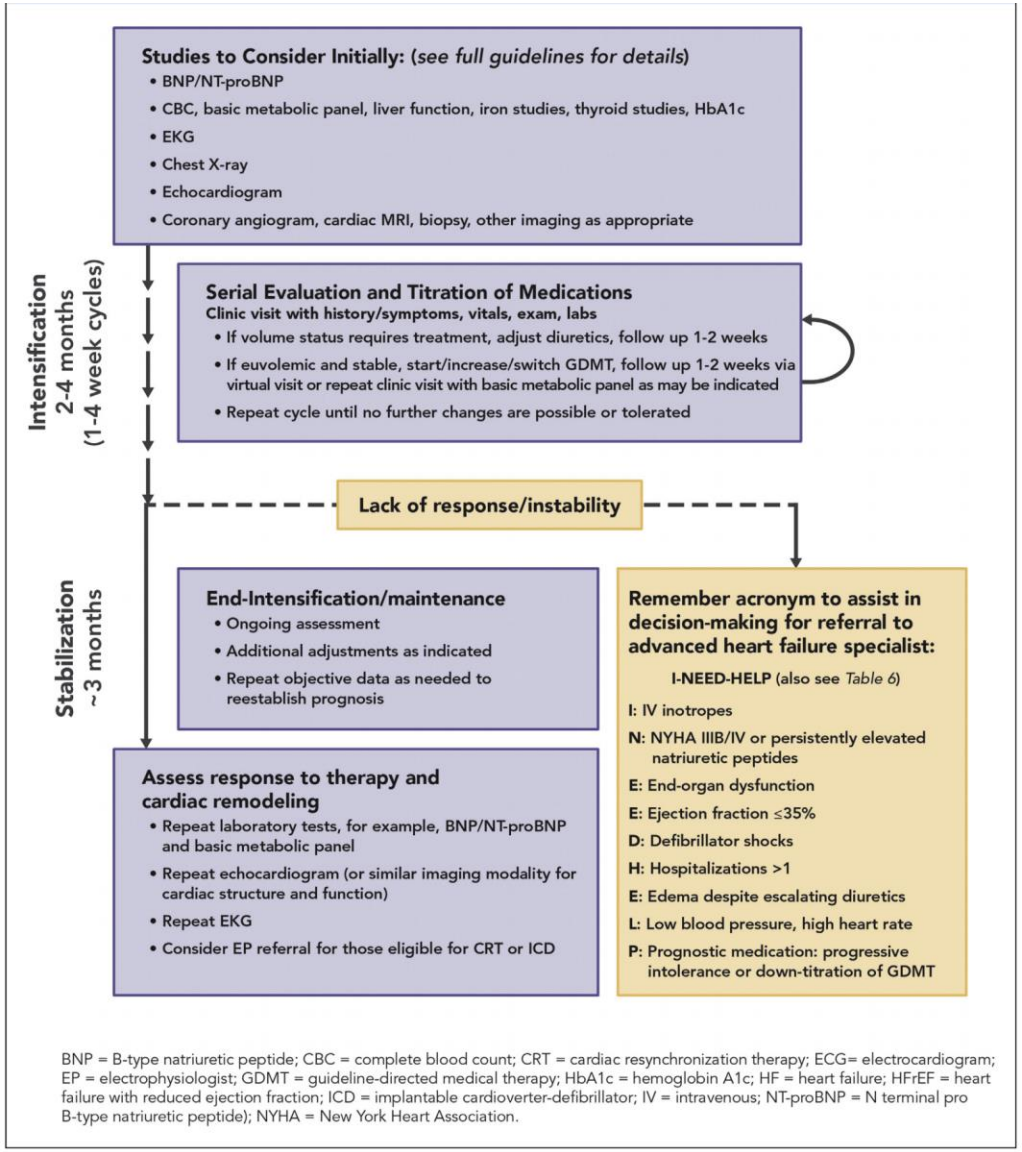
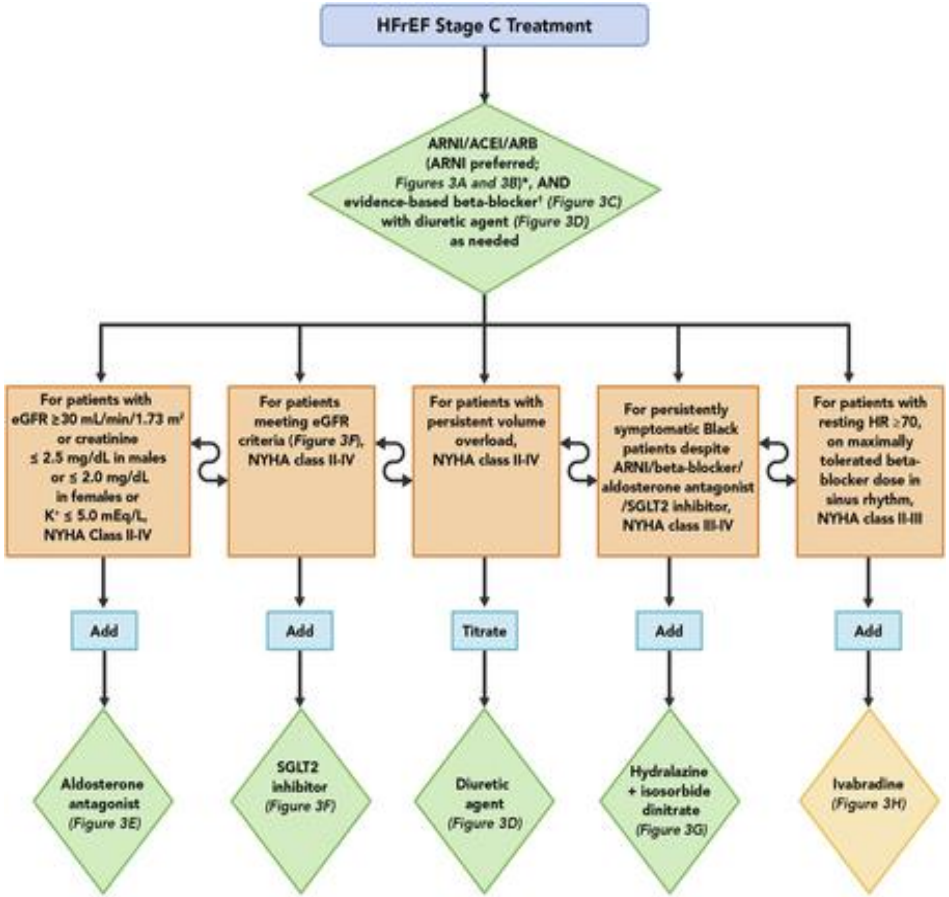
Testing and Medication Titration Following Diagnosis of HFrEF



BNP = B-type natriuretic peptide; CBC = complete blood count; CRT = cardiac resynchronization therapy; ECG= electrocardiogram; EP = electrophysiologist; GDMT = guideline-directed medical therapy; HbA1c = hemoglobin A1c; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IV = intravenous; NT-proBNP = N terminal pro B-type natriuretic peptide); NYHA = New York Heart Association.

Treatment Algorithm for Guideline—Directed Medical Therapy Including Novel Therapies



*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Thomas M. Maddox et al. *J Am Coll Cardiol* 2021; 77:772-810.

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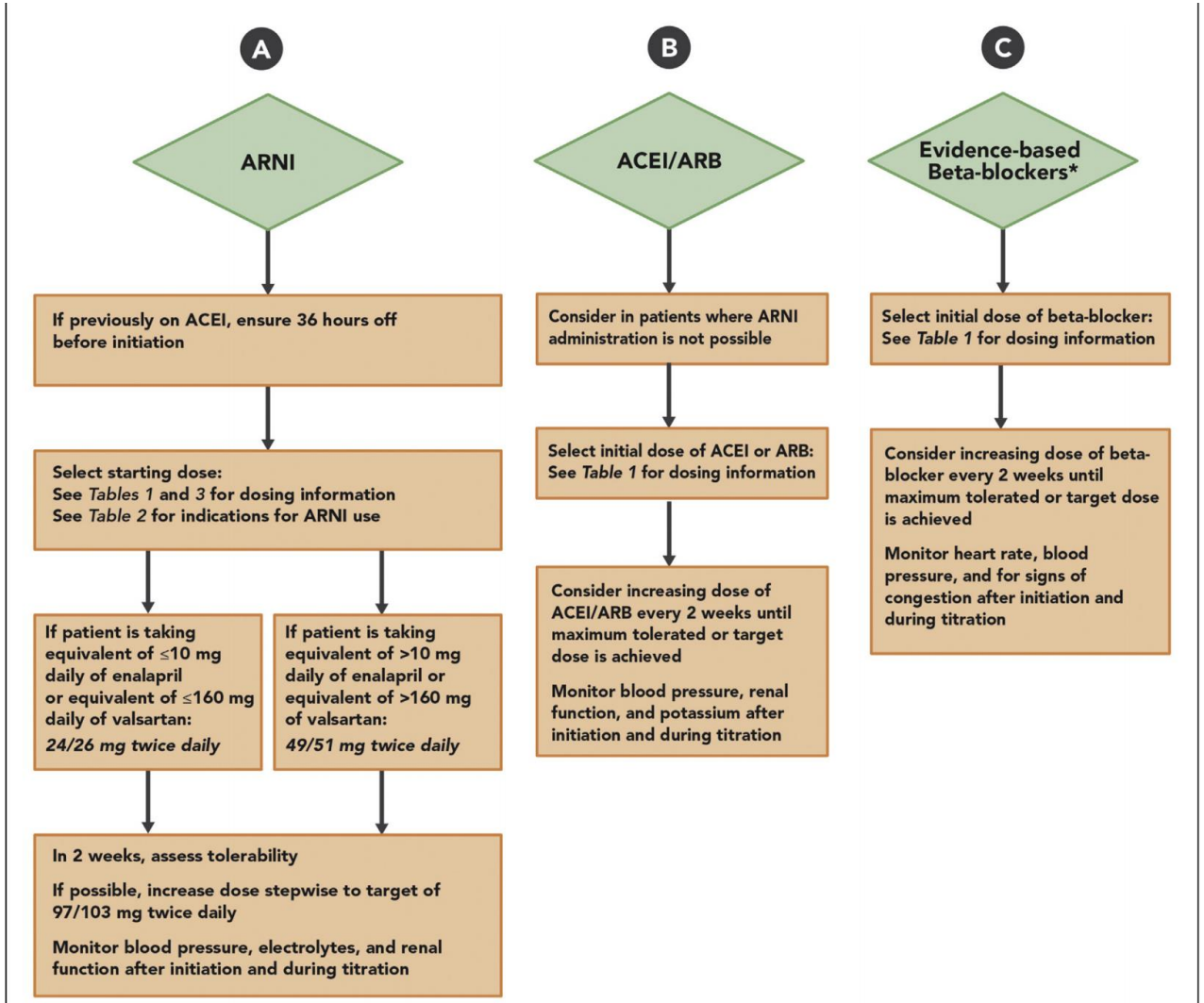
Guideline-Directed Medical Therapy

Including Novel Therapies in the Expert Consensus Decision Pathway for Chronic Heart Failure



ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate.

*Carvedilol, metoprolol succinate, or bisoprolol.

ARNIs are the preferred agents, but for patients in whom ARNI administration is not possible, an ACEI/ARB is recommended.

Thomas M. Maddox et al. *J Am Coll Cardiol* 2021; 77:772-810.

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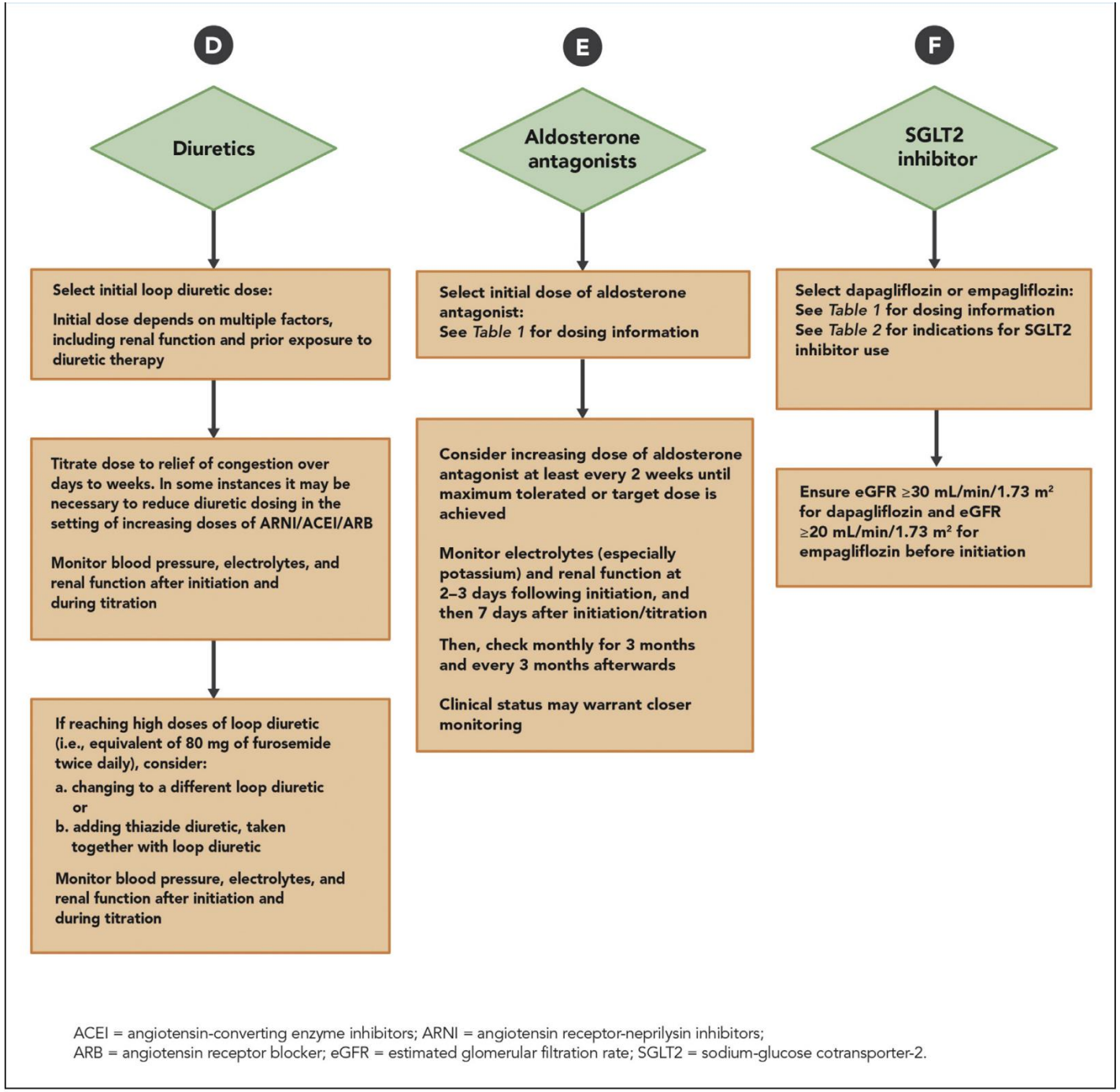
Guideline-Directed Medical Therapy

Including Novel Therapies in the Expert Consensus Decision Pathway for Chronic Heart Failure



ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter-2.

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Guideline-Directed Medical Therapy

Including Novel Therapies in the Expert Consensus Decision Pathway for Chronic Heart Failure

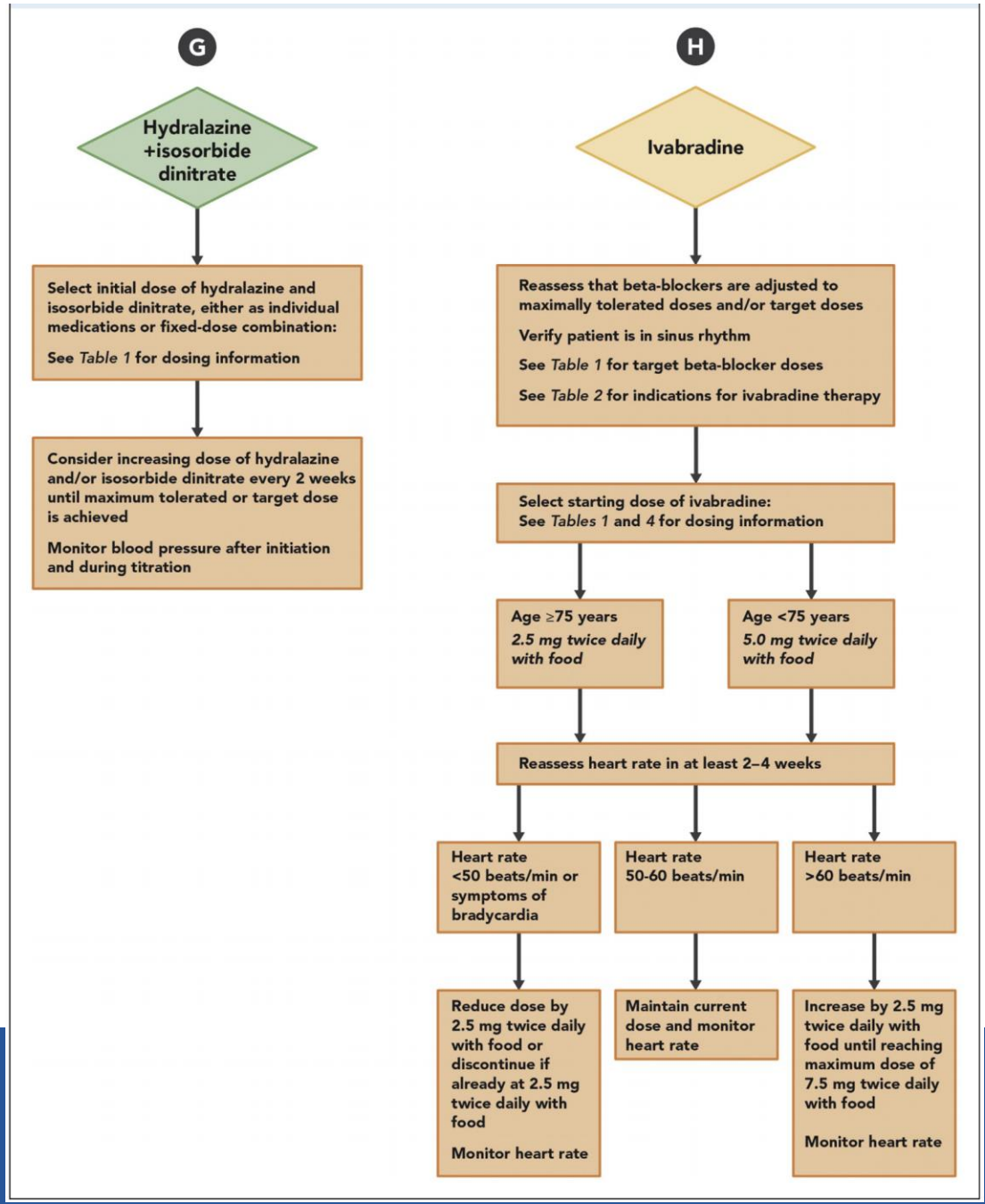

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TABLE 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF (choice and timing of each therapy and in whom they should be added discussed in the text)*

	Starting Dose	Target Dose
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5–25 mg daily	200 mg daily
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate†	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/hydralazine‡	20 mg/37.5 mg (1 tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5–5 mg twice daily	Titrate to heart rate 50–60 beats/min. Maximum dose 7.5 mg twice daily

*Digoxin remains indicated for HFrEF, but there are no contemporary data to warrant additional comment in this document. The reader is referred to already available guideline statements (3).

†Isosorbide mononitrate is not recommended by the ACC/AHA/HFSA guideline.

‡The ACC/AHA/HFSA guideline considers either the fixed-dose combination or the separate combination of isosorbide dinitrate and hydralazine as appropriate guideline-directed therapy for HF.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; SGLT2 = sodium-glucose cotransporter-2.

Indications for use of an:

1. ARNI,
2. Ivabradine,
3. SGLT2i

Indications for Use of an ARNI

- HFrEF (EF ≤40%)
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF in place of an ACEI or ARB

Indications for Use of Ivabradine

- HFrEF (EF ≤35%)
- On maximum tolerated dose of beta-blocker
- Sinus rhythm with a resting heart rate ≥70 beats/min
- NYHA class II or III HF

Indications for Use of an SGLT2 Inhibitor

- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF

ACEI = angiotensin-converting-enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

Population	Initial Dose
High-dose ACEI *> Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**49/51 mg twice daily**
High-dose ARB *> Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
De novo initiation of ARNI *Low- or medium-dose ACEI* *≤ Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**24/26 mg twice daily**
Low- or medium-dose ARB *≤ Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
ACEI/ARB naive	
*Severe renal impairment** *(eGFR <30 mL/min/1.73 m^2)*	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

*This population was not studied in the PARADIGM-HF trial. The statement is consistent with FDA-approved labeling indications.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI= angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF.

Contraindications and Cautions for Sacubitril/Valsartan, Ivabradine and SGLT2 Inhibitors

A) Sacubitril/Valsartan

Contraindications	Cautions
■ Within 36 hours of ACEI use ■ History of angioedema with or without an ACEI or ARB ■ Pregnancy ■ Lactation (no data) ■ Severe hepatic impairment (Child-Pugh C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARBs or ARNIs	■ Renal impairment: – Mild-to-moderate (eGFR 30-59 mL/ min/1.73 m^2): no starting dose adjustment required – Severe* (eGFR <30 mL/min/ 1.73 m^2): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Hepatic impairment: – Mild (Child-Pugh A): no starting dose adjustment required – Moderate (Child-Pugh B): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Renal artery stenosis ■ Systolic blood pressure <100 mm Hg ■ Volume depletion

B) Ivabradine

Contraindications	Cautions
■ HFpEF ■ Presence of angina with normal EF ■ Hypersensitivity ■ Severe hepatic impairment (Child-Pugh C) ■ Acute decompensated HF ■ Blood pressure <90/50 mm Hg ■ Sick sinus syndrome without a pacemaker ■ Sinoatrial node block ■ 2nd or 3rd degree block without a pacemaker ■ Resting heart rate <60 beats/min ■ Persistent AF or flutter ■ Atrial pacemaker dependence	■ Sinus node disease ■ Cardiac conduction defects ■ Prolonged QT interval

C) SGLT2 Inhibitors

Contraindications	Cautions
■ Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis ■ Known hypersensitivity to drug ■ Lactation (no data) ■ On dialysis	■ For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m^2 ■ For HF care, empagliflozin, eGFR <20 mL/min/1.73 m^2 ■ Pregnancy ■ Increased risk of mycotic genital infections ■ May contribute to volume depletion. Consider altering diuretic dose if applicable ■ Ketoacidosis in patients with diabetes: ■ Temporary discontinuation before scheduled surgery is recommended to avoid potential risk for ketoacidosis ■ Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level ■ Acute kidney injury and impairment in renal function: consider temporarily discontinuing in settings of reduced oral intake or fluid losses ■ Urosepsis and pyelonephritis: evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated ■ Necrotizing fasciitis of the perineum (Fournier's gangrene): rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise

*This population was not studied in PARADIGM-HF. The statement is consistent with FDA-approved labeling indications.

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FDA = Food and Drug Administration; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF; SGLT2 = sodium-glucose cotransporter-2.

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Recommended Starting Dose of Ivabradine

Population	Initial Dose
Maximally tolerated beta-blocker dose with persistent resting heart rate ≥70 beats/min	5 mg twice daily with meals
History of conduction defects Age ≥75 years	2.5 mg twice daily with meals

Triggers for Heart Failure Patient Referral to a Heart Failure Specialist/ Program

Clinical Scenario	
	1. New-onset HF (regardless of EF): Refer for evaluation of etiology, guideline-directed evaluation and management of recommended therapies, and assistance in disease management, including consideration of advanced imaging, endomyocardial biopsy, or genetic testing for primary evaluation of new-onset HF
	2. Chronic HF with high-risk features, such as development or persistence of one or more of the following risk factors: ■ Need for chronic intravenous inotropes ■ Persistent NYHA functional class III-IV symptoms of congestion or profound fatigue ■ Systolic blood pressure ≤90 mm Hg or symptomatic hypotension ■ Creatinine ≥1.8 mg/dL or BUN ≥43 mg/dL ■ Onset of atrial fibrillation, ventricular arrhythmias, or repetitive ICD shocks ■ Two or more emergency department visits or hospitalizations for worsening HF in the prior 12 months ■ Inability to tolerate optimally dosed beta-blockers and/or ACEI/ARB/ARNI and/or aldosterone antagonists ■ Clinical deterioration, as indicated by worsening edema, rising biomarkers (BNP, NT-proBNP, others), worsened exercise testing, decompensated hemodynamics, or evidence of progressive remodeling on imaging ■ High mortality risk using a validated risk model for further assessment and consideration of advanced therapies, such as the Seattle Heart Failure Model
	3. Persistently reduced LVEF ≤35% despite GDMT for ≥3 months: refer for consideration of device therapy in those patients without prior placement of ICD or CRT, unless device therapy is contraindicated or inconsistent with overall goals of care
	4. Second opinion needed regarding etiology of HF; for example: ■ Coronary ischemia and the possible value of revascularization ■ Valvular heart disease and the possible value of valve repair ■ Suspected myocarditis ■ Established or suspected specific cardiomyopathies (e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Chagas disease, restrictive cardiomyopathy, cardiac sarcoidosis, amyloid, aortic stenosis)
	5. Annual review needed for patients with established advanced HF in which patients/caregivers and clinicians discuss current and potential therapies for both anticipated and unanticipated events, possible HF disease trajectory and prognosis, patient preferences, and advanced care planning
	6. Assessment of patient for possible participation in a clinical trial

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; BUN = blood, urea, nitrogen; CRT = cardiac resynchronization therapy; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Essential Skills for a Heart Failure Team

- HF diagnosis and monitoring for progression
- Treatment prescription, titration, and monitoring
- Patient and caregiver education on disease and treatments
- Lifestyle prescription (e.g., diet, exercise), education, and monitoring
- Psychological and social support assessment, treatment, and monitoring
- Palliative and end-of-life counseling and care
- Coordination of care for concomitant comorbidities

HF = heart failure.

Potential Infrastructure Components to Support Team-Based Heart Failure Care

Modality	Challenges	Potential Benefits
Electronic health records	■ Ease of access ■ Interoperability with other electronic data repositories ■ Data accuracy including missing data	■ Reduction in errors ■ Decision support (e.g., ACC TreatHF mobile app) ■ Accurate medication reconciliation to facilitate guideline adherence ■ Patient portal to facilitate patient/caregiver engagement, including patient-reported outcomes and other patient-generated data (if available)
Patient monitoring devices: (e.g., scales, implanted devices, bioimpedance devices, wearable hemodynamic sensors)	■ Accuracy ■ False alert ■ Cost-effectiveness ■ Infrastructure/resource needs, including accurate data management and triage	■ Early warning and a reduction in morbidity
Wearable activity monitors	■ Accuracy	■ Physical activity coaching/adherence ■ Early detection of arrhythmias (e.g., AF)
Smartphones or other mobile technologies	■ Need for more useful apps or other mobile technologies, including support systems in place for providing equipment and training for use ■ Potential privacy issues	■ Activity tracking ■ Diet records ■ Weight management ■ Communication with HF team ■ Prompts for medication and lifestyle adherence

ACC = American College of Cardiology; AF = atrial fibrillation; HF = heart failure.

Reasons for Nonadherence (World Health Organization)

Patient	■ Perceived lack of effect ■ Poor health literacy ■ Physical impairment (vision, cognition) ■ Mental health conditions (depression, anxiety) ■ Social isolation ■ Cognitive impairment (dementia)
Medical condition	■ High HF regimen complexity ■ Impact of comorbidities (e.g., depression) ■ Polypharmacy due to multiple comorbidities
Therapy	■ Frequency of dosing ■ Polypharmacy ■ Side effects
Socioeconomic	■ Out-of-pocket cost ■ Difficult access to pharmacy ■ Lack of social support ■ Homelessness
Health system	■ Poor communication ■ Silos of care ■ No automatic refills ■ Difficulty navigating patient assistance programs

HF = heart failure.

Ten Considerations to Improve Adherence

1. Capitalize on opportunities when patients are most predisposed to adherence
■ In-hospital/pre-discharge initiation following decompensation
2. Consider the patient's perspective
■ Start with the goals of therapy (feeling better and living longer) and then discuss how specific actions (medication initiation, intensification, monitoring, and adherence) support those goals (example: ACC's My Heart Failure Action Plan)
■ Use decision aids when available (example: CardioSmart Heart Failure Resources)
■ Ask patient how they learn best and provide education accordingly
■ Use culturally relevant patient education materials
3. Simplify medication regimens whenever possible
4. Consider costs and access
■ Become familiar with and advocate for systems that help make cost sharing automatic, immediate, and transparent
■ Prescribe lower-cost medications if of similar efficacy
■ Facilitate access to copay assistance
■ Discuss out-of-pocket copays proactively ■ Prescribe 90-day quantities for refills
5. Communicate with other clinicians involved in care, ideally facilitated by electronic health records
6. Educate using practical, patient-friendly information
■ Provide a written explanation of the purpose of each medication prescribed
■ Plan pharmacist visits for complex medication regimens
■ Use the "teach back" principle to reinforce education
7. Recommend tools that support adherence in real time
■ Pill boxes to be filled by patient or care partner a week at a time
■ Alarms for each time of the day medications are due
■ Smartphone or other mobile health applications that provide an interactive platform for education, reminders, warnings, and adherence tracking
8. Consider behavioral supports
■ Motivational interviewing
■ Participate in engaged benefit designs
9. Anticipate problems
■ Communicate common side effects
■ Provide instructions on when to call for refills or report problems
■ Remind patients using pharmacy assistance programs that refills/reorders are not automatic
10. Monitor adherence and target patients at risk
■ Inquire patients directly (e.g., "How many times in a week do you miss taking your medications?" "Have you run out of your medications recently?")
■ Carry out medicine reconciliation at visits, with focus on discrepancies
■ Assess remaining dosage units (i.e., count excess remaining tablets)
■ Monitor pharmacy fills, using available clinical databases or automated alerts for failed fills and refills
■ Review available drug levels (e.g., digoxin, INR) or concentrations of BNP/NT-proBNP
■ Plan home-based nursing visits for appropriate patients

ACC = American College of Cardiology; BNP = B-type natriuretic peptide; INR = international normalized ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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Specific Patient Cohorts in Heart Failure Care

Patient Cohorts	Description	Evidence-based recommendations	Risks	Uncertainties
African-American patients	Self-identified	GDMT	■ ARNIs, ACEIs, and ARBs: possibly higher risk of angioedema compared with Caucasian patients ■ Uncertain risk of hypotension when combining new drugs with HYD/ISDN	Expected outcomes of ARNI, SGLT2 inhibitors, and/or ivabradine in those treated with HYD/ISDN
Older adults	≥75 years of age	■ GDMT, but recognize that this population is excluded from many trials supporting GDMT ■ Consider starting with lower doses of GDMT	■ Potential falls ■ Worsening of renal function ■ Polypharmacy ■ Comorbidity	Efficacy of lower-dose GDMT on outcomes
Frail patients	Meets established frailty criteria (134)	GDMT as tolerated	■ Uncertain response to GDMT ■ Possibly increased risk for adverse drug reactions	Ability to have an impact on natural history in the frail with HF

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HYD/ISDN =hydralazine/isosorbide dinitrate.

Strategies to Reduce Patients' Cost of Care

- Coordinate care (including labs and imaging) among clinicians to minimize unnecessary duplication
- Consider limitations of medication coverage (insurance, Medicaid, etc.) when prescribing
- Use generic equivalents for GDMT whenever possible
- Work with a pharmacist, social worker, or patient navigator to identify and navigate Patient Assistance Programs
- Request price matching if a drug is found at a lower cost at another pharmacy

GDMT = guideline-directed medical therapy.

Helpful Information for Completion of Prior Authorization Forms

Patient Criteria
■ Include HF phenotype: HFrEF; HFpEF
■ Identify NYHA functional class
■ Include recent measurement of LVEF with source documentation if requested
■ Identify the treatment requested or the additional testing required, with indications supported by evidence and/or guideline statements where applicable; clinical judgment, especially for testing requests, is an appropriate rationale
■ Address previous therapies used and the rationale for switching to or adding the requested treatment
■ Address known contraindications to use, adverse effects, and steps intended to minimize the risks of drugs or procedures
■ Document, when appropriate, that delays or interruptions in therapy may cause harm to the patient
■ Work with local pharmacy resources and pharmacy professionals to jointly address prior authorization requirements; do not hesitate to appeal decisions that are contrary to the best patient care. Document all steps taken in the patient's health record.

*Required information may vary depending on payer and state.

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

UCI Health Advance Heart Failure & VAD Program

- Our Advanced HF Program also offer state-of-the-art treatments, including the latest drugs, PA pressure remote monitoring, Extracorporeal Membrane Oxygenation (ECMO), heart pumps like left ventricular assist device (LVAD), and daily assess to our advanced HF clinic.
- Goal to:
  - Partner with our community providers in the care of Advanced HF patients
  - Make it easy for OC patients and their families to get advance HF Treatments locally
  - Provide full work-up for VAD and Heart Transplant
  - Collaborate with Transplant Center
  - Participate in shared care with our community providers

Our MCS TEAM

Acute Critical Care Anesthetist Medical Dir.

Dr. Kay Togashi, MD

CT Surgery Program Director

Dr. Jack Sun, MD
CT Surg. Program Director

Advanced Heart Failure-MCS Leadership

Dr. Fabio Sagebin, MD
MCS Surgical Dir.

Dr. Dawn Lombardo, DO
Advanced HF-MCS Medical Dir.

Advanced Heart Failure Cardiologists

Dr. Andy Lee, MD

Dr. Behram Mody, MD

CT Surgery Advanced Practice Providers and Nurse

Hector Gonzalez, PA

Recruiting, PA

Alessandra Caceres, NP

Recruiting, NP

Paula Ensley, RN
CT Surg. Nurse navigator

Nathalie De Michelis, RN
Advanced HF-MCS Program Mgr.

Advanced Heart Failure-MCS Advanced Practice Providers

Pedro Portes, NP

Katie Tran, NP

Carmina Inductivo, NP

Tamara Chaker, NP

Carrie Mitchell
VAD Financial Counselor

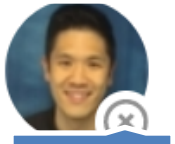
RNs LVAD Coordinators

Joey Rodriguez, RN
VAD Coordinator Sup.

Eunice Yi, , RN
VAD Coordinator

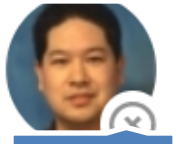
Acute Critical Care Anesthesiologists

Dr. Sonali Rao, MD
ACCM

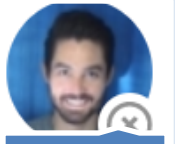


Dr. Howard Zee, MD
ACCM

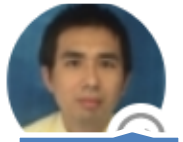
Dr. Trung Vu, MD
ACCM



Dr. **Gregory Yoshikawa,** MD, ACCM



Dr. Samuel W. Hong, MD, ACCM



Dr. Phat T. Dang, MD, ACCM

Dr. Govind Rajan, MD
ACCM

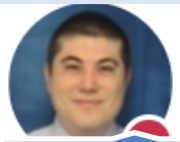
Dr. Jennifer Elia, MD
ACCM

Dr. Karen H. Katrivesis, MD ACCM

Dr. Jay Shen, MD ACCM

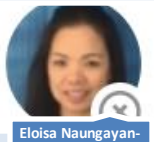
Palliative Care Providers

Dr. Shito Ito, MD

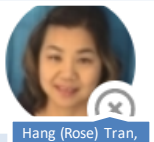


Dr. Lucas Puttock, DO

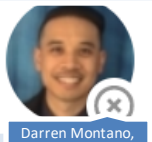
Acute Critical Care NPs



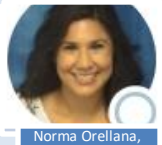
Eloisa Naungayan-Ramirez, ACCM NP



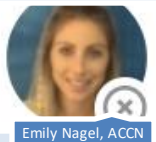
Hang (Rose) Tran, ACCM NP



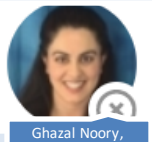
Darren Montano, ACCM NP



Norma Orellana, ACCM NP



Emily Nagel, ACCN NP



Ghazal Noory, ACCM NP

MCS Specialist Team Members

Dr. Hannah Nam, MD
Infectious Diseases

Dr. Cyrus Dastur, MD
Neurology

Dr. Ramy Hanna, MD
Nephrology

Dr. Jason Samarasena, MD
Gastroenterology

Dr. Richard Lee, MD
Pulmonary

MCS Specialist Team Members

Alan Pan, RN
MCS Case Manager

Connie Molitor, RN
MCS Case Manager

Bethzaira Garibay
MCS Social Worker

Lan Vu, PharmD
IP MCS Pharmacist

Connie Abdo, PharmD
OP MCS Pharmacist

Christine Cadiz, PharmD
OP MCS Pharmacist

Jade Yang, RD
MCS Dietician

Suzanne Baily
Physiotherapist Sup.

Breanne Israwi
Physiotherapist Sup.

Christina Ma Araneta
MCS Physiotherapist

Jovani Rioja, RN
MCS Unit Nurse representative

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Questions?

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