Is It Time to Treat Heart Failure Like Cancer

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1

Disclosure

Consultant: Alnylam; Boehringer Ingelheim; BridgeBio

Speakers' Bureau: Alnylam; Boehringer Ingelheim; BridgeBio

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Objectives

- To understand the high mortality rate associated with a heart failure diagnosis
- To be able to explain the pathophysiologic mechanisms that contribute to the mortality rate associated with heart failure with reduced ejection fraction (HFrEF)
- After hearing the presentation, the participant should be able to apply referral guidelines for Advanced Heart Cardiology to their practice

3

Case

35 y/o woman is admitted for observation to the hospital with progressively worsening right chest tenderness. On exam she is noted to have a palpable mass on the R breast. CT chest and mammogram reveal a 3 x 3 cm lesion concerning for malignancy.

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2020 Estimates

Estimated New Cases

Male			Female		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All sites	**893,660**		**All sites**	**912,930**	

Estimated Deaths

Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	**321,160**		**All sites**	**285,360**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

5

Cancer

- According to the NIH National Cancer Institute Cancer Trends Progress Report the death rate for all cancers combined in 2016 was 155.7/100,000
- There are therapies (most curative) for cancer if caught early enough
- Most cancers are treated by an Oncologist
- Oncology consultations tend to be triggered by radiology once lesions are discovered and do not wait for primary physician to refer

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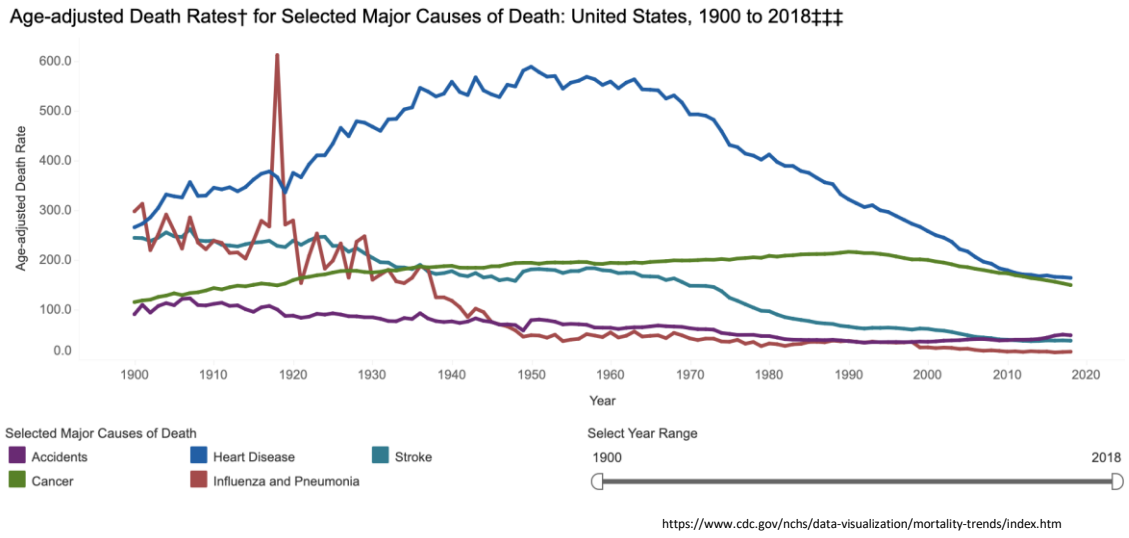
So, Is Heart Failure as Deadly as Cancer?

7

Heart Disease #1 Cause of Death



https://www.cdc.gov/nchs/data-visualization/mortality-trends/index.htm

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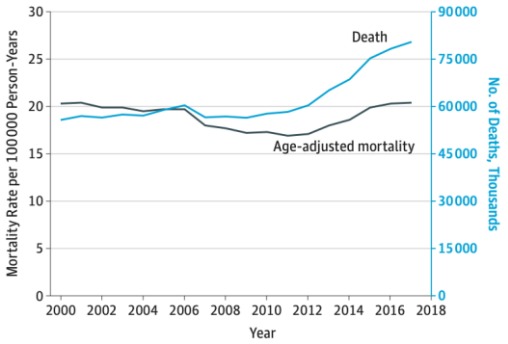
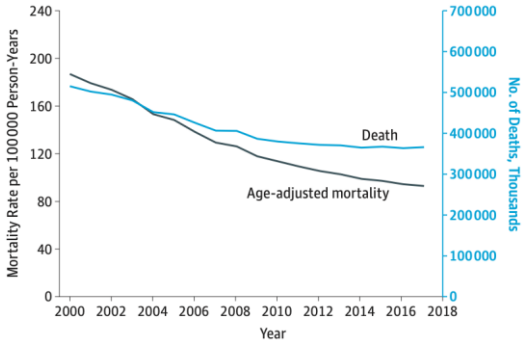
US Heart Disease Mortality Rates 1/1/2011 – 12/31/2017

HEART FAILURE MORTALITY
INCREASED 20.7%



CORONARY HEART DISEASE
DECREASED BY 14.9%



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.

9

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]

10

US Heart Failure Statistics

- **"With the number of adults aged 65 years and older projected to increase an additional 44% from 2017 to 2030, innovative and effective approaches to prevent and treat HD, particularly the substantially increasing rates of heart failure, are needed" (Sidney et al JAMA Cardiol 2019)**

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]

11

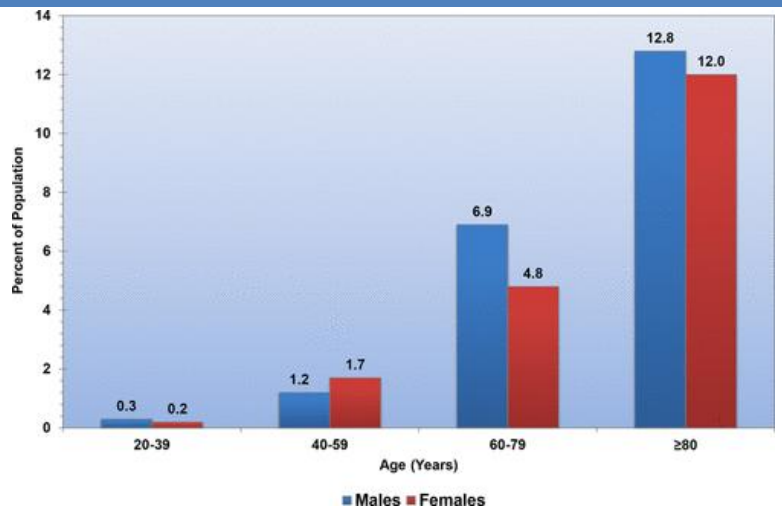
US Heart Failure (HF) Statistics

- **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.

12

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)

13

Heart Failure Hospitalizations Increase Mortality

Mortality Associated w/ HF Hospitalization

- 30-day mortality 10.4%
- 1-year mortality 22.0%
- 5-year mortality 42.3%

Loehr LR, Rosamond WD, Chang PP, et al. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am JCardiol. 2008;101:1016–22

14

Heart Failure Hospitalizations Increase Mortality

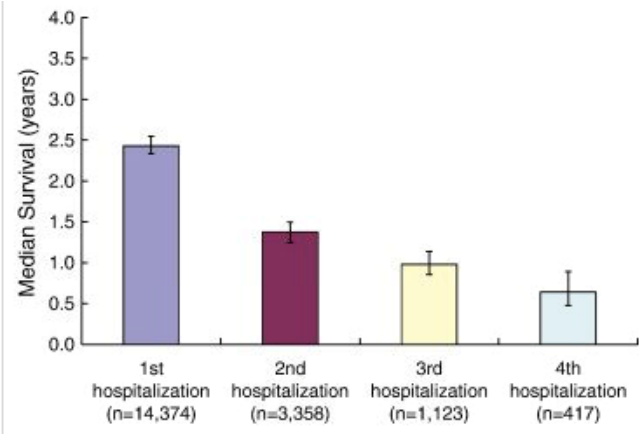
14,374 Patients Hospitalized w/ New Dx of Heart Failure in British Colombia, Canada 2000 – 2004

- 7401 patients died during the follow up period
- The 30-day all-cause mortality after the first HF hospitalization was 12%, and the 1-year mortality was 34%
- The median survival (50% mortality) was 2.4 years
- Significant increase in all-cause mortality with advanced age

Setoguchi S, Stevenson L, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007 Aug;154(2):260-6

15

Heart Failure Hospitalizations Increase Mortality



Setoguchi S, Stevenson L, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007 Aug;154(2):260-6

16

Heart Failure Hospitalizations Increase Mortality

Mortality Significantly ↑ After Each Additional HF Hospitalization

- Median survival times after each HF hospitalization
  - **First** **2.4 years (95% CI 2.3-2.5)**
  - **Second** **1.4 years (95% CI 1.2-1.5)**
  - **Third** **1.0 years (95% CI 0.9-1.1)**
  - **Fourth** **0.6 years (95% CI 0.5-0.9)**
- Most patients were alive 2 years after the first HF hospitalization, but approximately half were dead by 1 year after 3 hospitalizations

Setoguchi S, Stevenson L, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007 Aug;154(2):260-6

17

Why Is Heart Failure So Deadly

Review of Heart Failure Pathophysiology

18

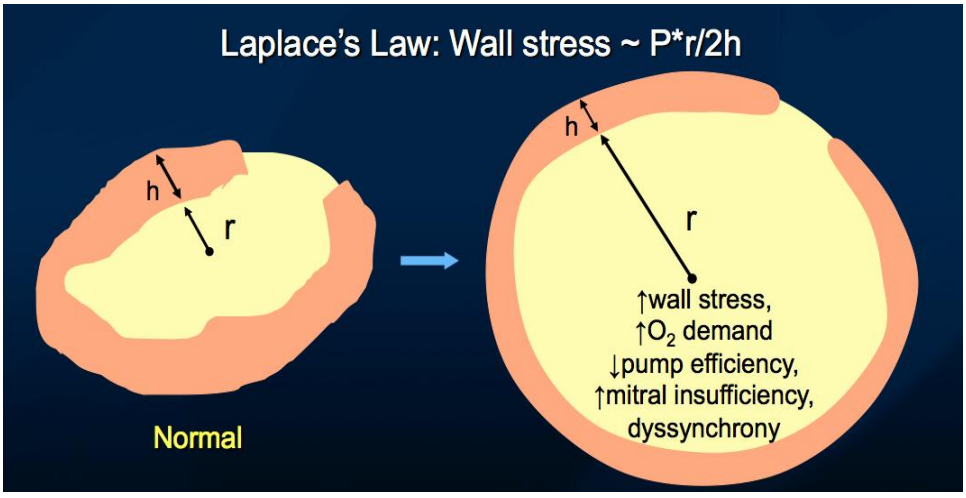
HFrEF Hemodynamics

Activation Neurohormonal Cascade

- Sympathetic nervous system (SNS)
- Renin-angiotensin-aldosterone system (RAAS)
- Arginine-vasopressin (AVP) and endothelin (ET) axis

19

Chronic Neurohormonal Activation

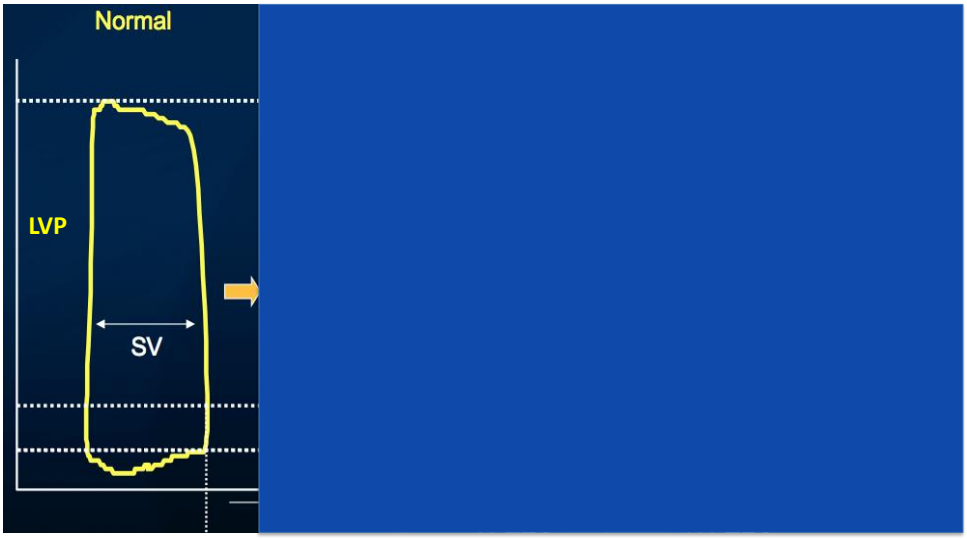


Normal Heart **Heart Failure With Reduced Ejection Fraction**

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

20

Systolic Dysfunction Stage Progression



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

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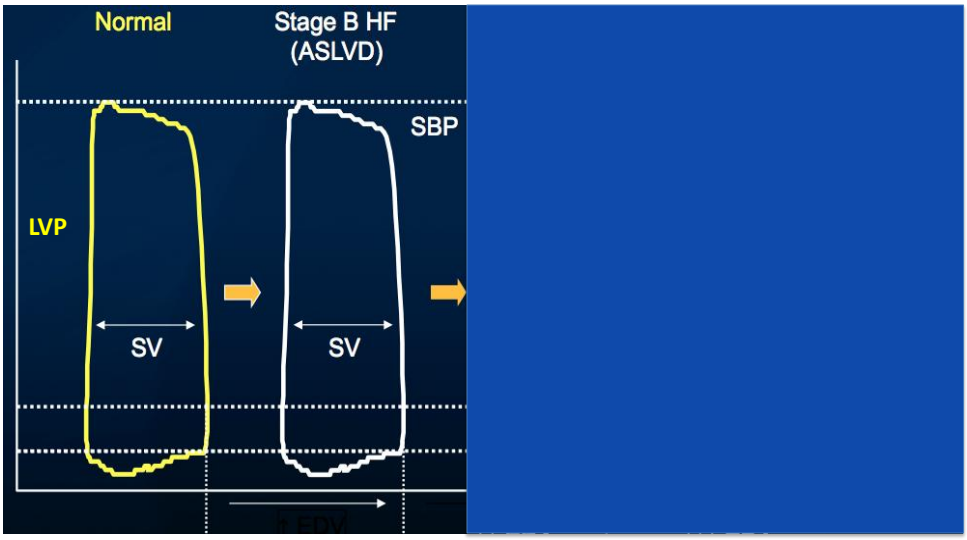
Systolic Dysfunction Stage Progression



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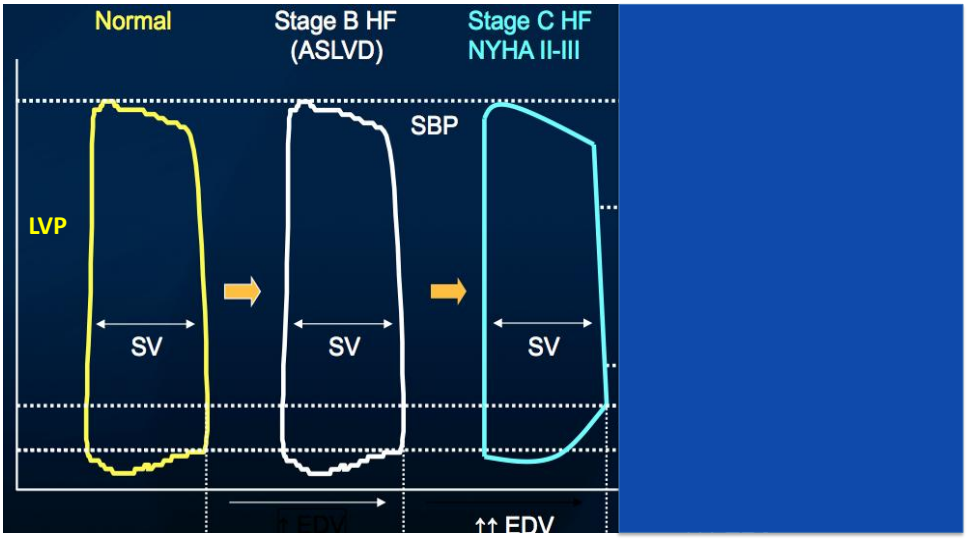

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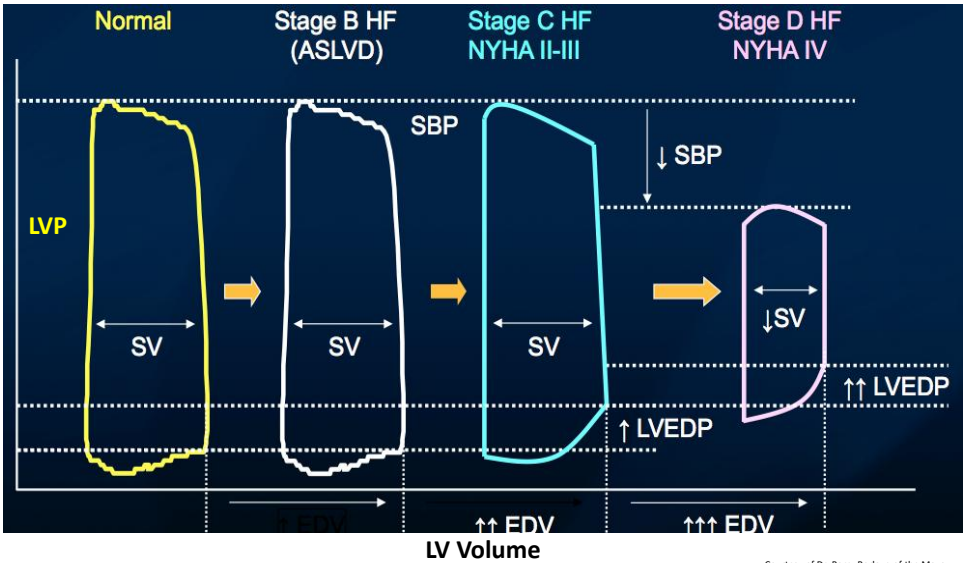
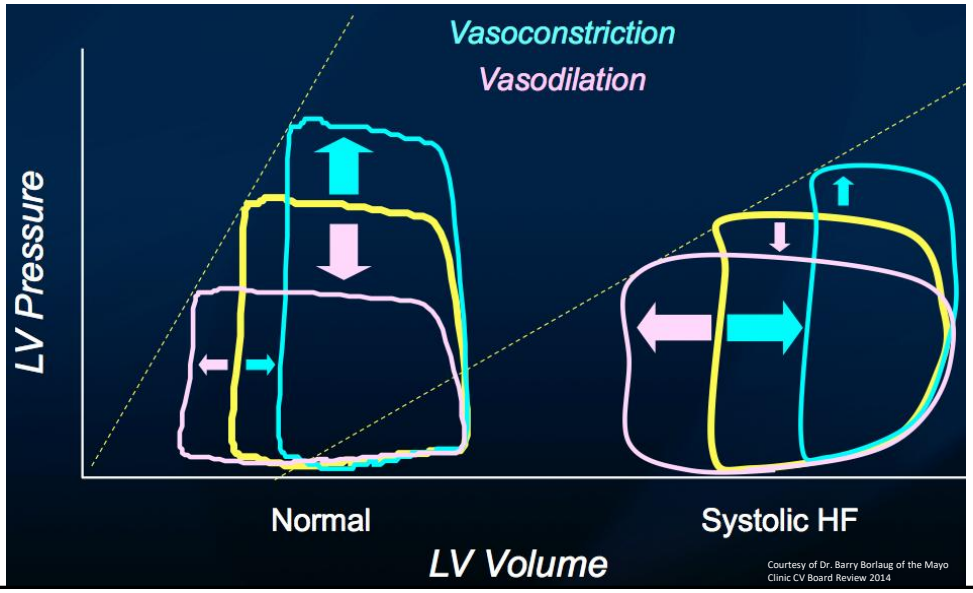


Courtesy of Dr. Barry Borlaug of the Mayo Clinic CV Board Review 2014

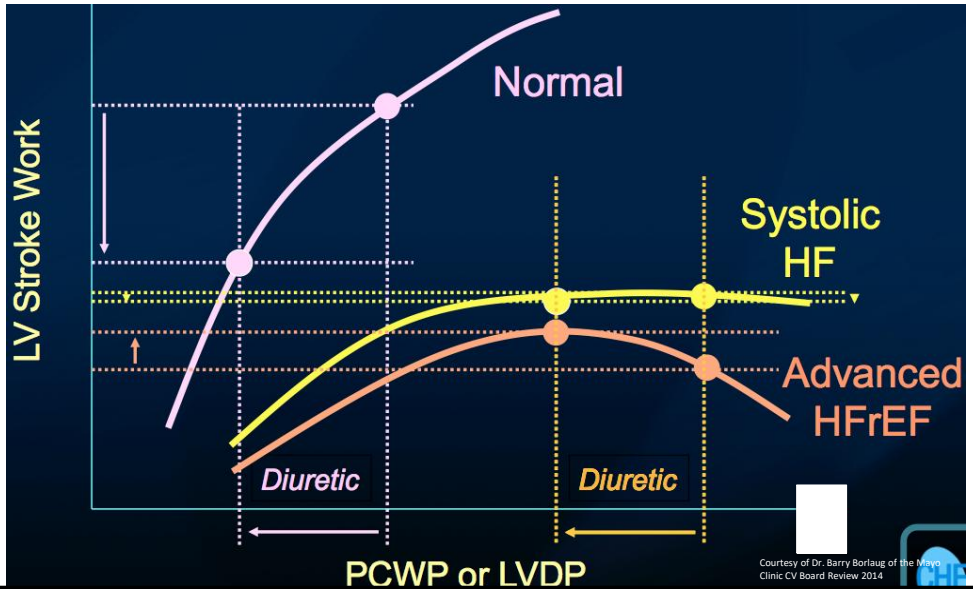
24

Afterload Sensitivity of HFrEF



25

Preload Sensitivity of HFrEF



26

Signs & Symptoms of Heart Failure

	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

27

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.

28

History & Physical Predictors of HF

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29

Classification of Heart Failure

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

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

30

ACC/AHA Heart Failure Stages

Stage A
High risk without structural disease

→

Stage B
Structural disease without symptoms

→

Stage C
Structural disease with symptoms

→

Stage D
Refractory, end-stage heart failure

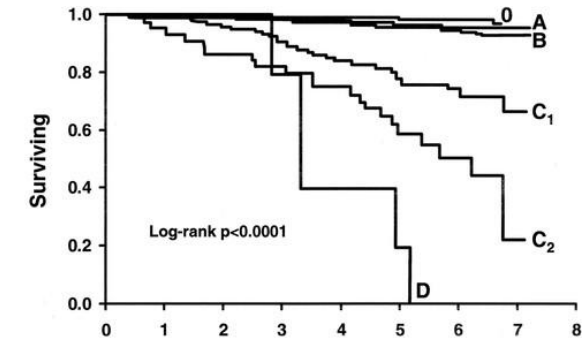
Main goals:

Relieve symptoms, prevent progression, reduce mortality

Hunt et al. 2009 ACC/AHA Guidelines. J Am Coll Cardiol 2009;53:e1-90.

31

Survival By ACC/AHA Stage of HF



# at risk								
Stage 0	640	640	639	637	635	464	218	34
A	454	453	451	449	446	322	133	22
B	691	687	685	677	673	475	239	29
C_1	195	193	187	178	166	114	54	5
C_2	44	42	38	36	33	18	8	1
D	5	5	5	4	2	1	0	0

Khawaja Afzal Ammar. Circulation. Prevalence and Prognostic Significance of Heart Failure Stages, Volume: 115, Issue: 12, Pages: 1563-1570, DOI: (10.1161/CIRCULATIONAHA.106.666818)

32

OPTIME Study

No survival benefit with Milrinone in Stage D HF

	Placebo	Milrinone
• Death or readmit within 60 days	35.3%	35.0%
• Mean # days of hosp within 60 days	13.5	13.4
• Death within 60 days	8.9%	**10.3%**

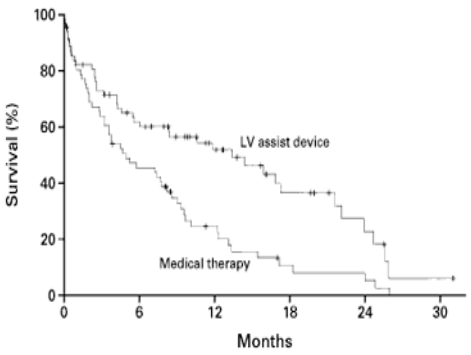
JAMA 2002;287:1541

33

REMATCH

Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

- Randomized clinical trial of **Optimal Medic**
- Non-transplant candidates (n=129)
  - EF ≤ 25%
  - peak VO2 < 12 ml/kg/min
  - or continuous infusion inotropes
- **25% One Year Survival in Medical Therapy**
- FDA approval for XVE as destination therapy



No. at Risk						
LV assist device	68	38	22	11	5	1
Medical therapy	61	27	11	4	3	0

Rose E, Gelijns A, Moskowitz A, et al. Long-term use of a left ventricular assist device for end stage heart failure. N Engl J Med 2001; 345:1435-43

34

REMATCH

Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

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- Non-transplant candidates (n=129)
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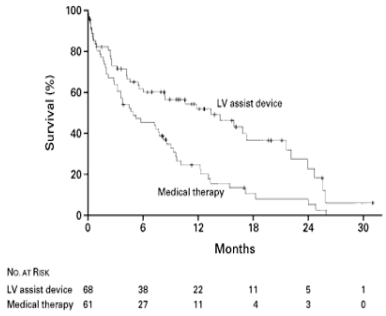

Rose E, Gelijns A, Moskowitz A, et al. Long-term use of a left ventricular assist device for end stage heart failure. N Engl J Med 2001; 345:1435-43

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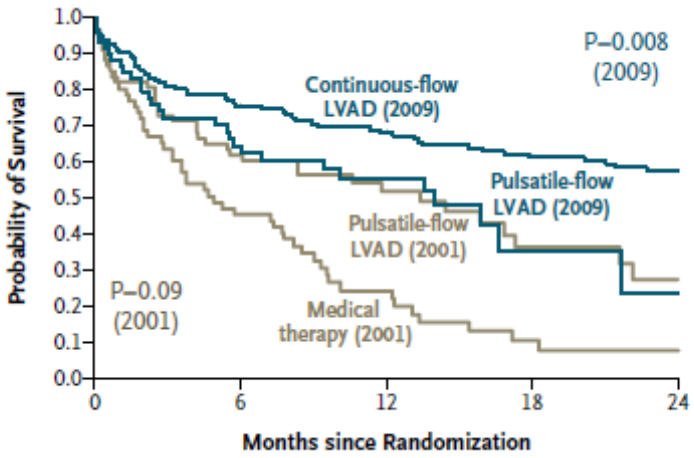
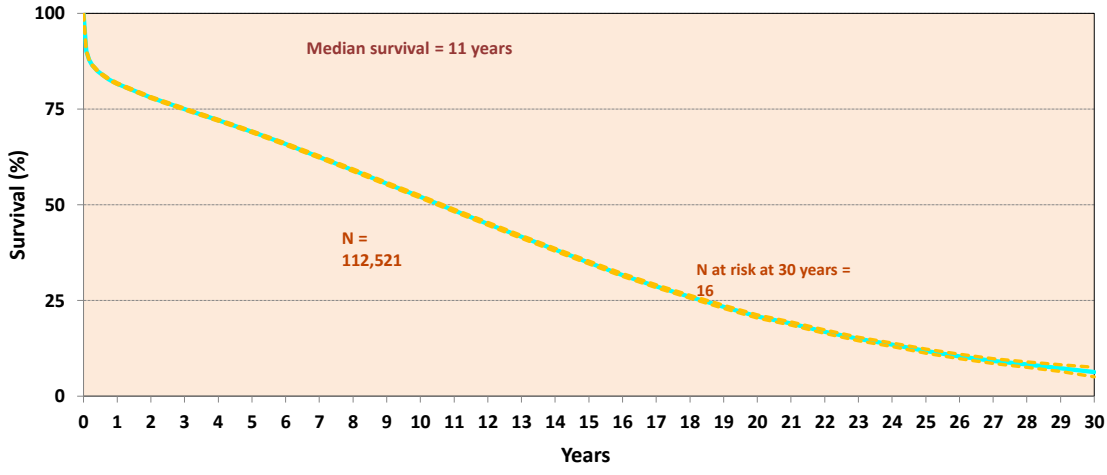
Survival Rates for LVADs versus Medical Therapy



Fang JC NEJM 2009;361

36

Adult and Pediatric Heart Transplants Kaplan-Meier Survival
(Transplants: January 1982 – June 2013)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
JHLT. 2015 Oct; 34(10): 1244-1254

37

Strategies of Heart Failure Treatment

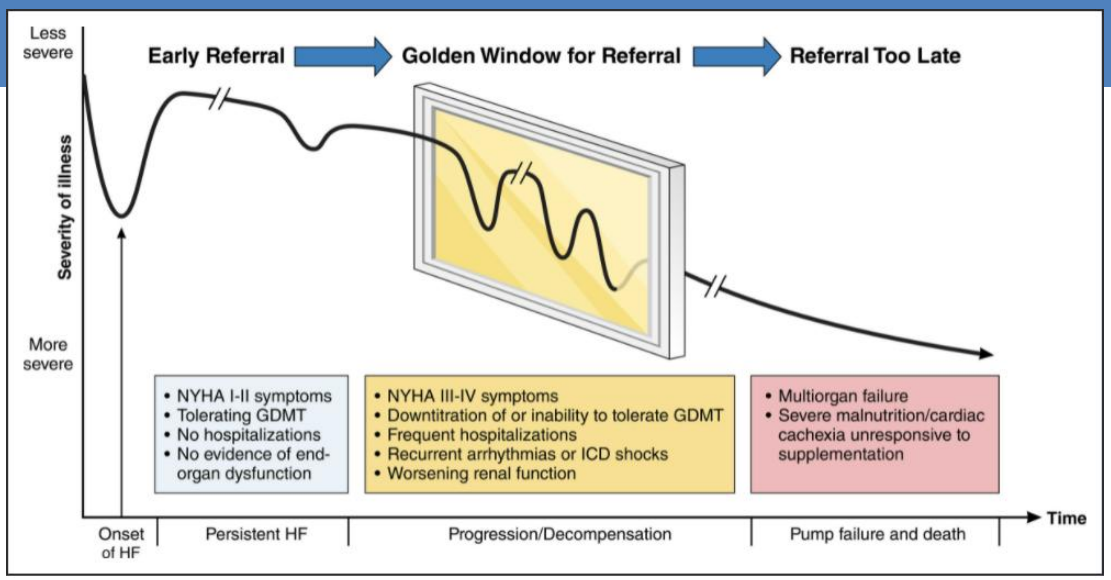
- Determine the Ejection Fraction
- Monitor for heart failure medication intolerance
- Look for easily reversible causes
  - Coronary Disease (Stress test, Calcium Score)
  - Metabolic (TSH, Ferritin, etc)
  - Drug (Amphetamine/cocaine) or ETOH abuse
  - Arrhythmia (ECG)
- If LVEF ≦ 40% Refer to HF Cardiologist or General Cardiologist

38

Timing of Referral to Heart Failure Cardiologist

- Earlier is better
- Prevents chance of multiorgan damage
- Patient has a better opportunity to become a Transplant recipient

39



Morris A et al Circ 2021

40

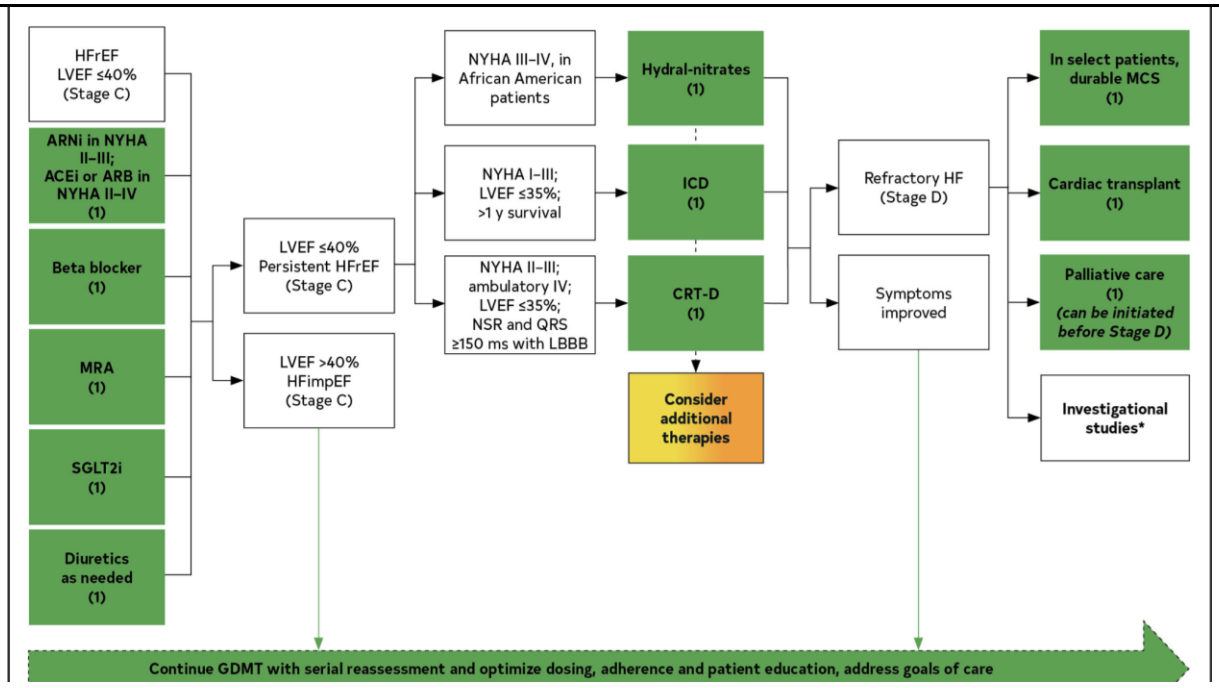
Circulation
Volume 144, Issue 15, 12 October 2021; Pages e238-e250
https://doi.org/10.1161/CIR.0000000000001016

AHA SCIENTIFIC STATEMENT

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

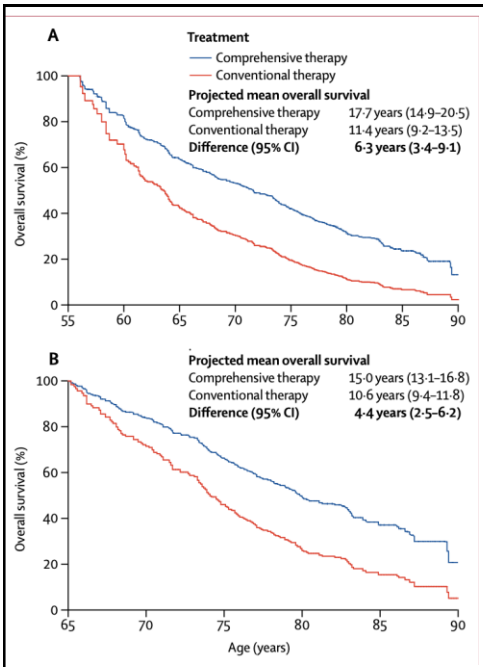
Alanna A. Morris, MD, MSc, FAHA, Chair, Prateeti Khazanie, MD, MPH, Vice Chair, Mark H. Drazner, MD, MSc, Vice Chair, Nancy M. Albert, PhD, Khadijah Breathett, MD, MS, FAHA, Lauren B. Cooper, MD, MHS, Howard J. Eisen, MD, Patrick O'Gara, MD, Stuart D. Russell, MD, and on behalf of the American Heart 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

41



Heidenreich et al Circ 2022

42



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.

43

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

44

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

45

Case

35 y/o woman is admitted for observation to the hospital with progressively worsening right chest tenderness. On exam she is noted to have a palpable mass on the R breast. CT chest and mammogram reveal a 3 x 3 cm lesion concerning for malignancy.

What Is the Next Step?

A. Send her home and tell her to follow up with her PCP
B. Refer her to a PCP that sees a lot of patients with cancer
C. Treat Conservatively, do not refer to a specialist
D. Consult Oncologist immediately to determine diagnostic (FNA, resection, LN biopsy) and Treatment course (Mastectomy, chemotherapy, radiation, lumpectomy, LN biopsy, etc.)