Understanding Heart Failure
HFrEF and Advanced Heart Failure

DEEPTHI MOSALI, MD, FACC
Objectives

- Review pathophysiology of HFrEF
- Briefly touch on Guidelines
- Understand the concept of Advanced Heart Failure and recognize it
Clinical Vignette

- 70 y/o female with CMY related chemotherapy (breast Ca)
- Increasing symptoms of HF
- Admissions: 4/16, seen in the office 5/3, set up for BiV 7/17 (cancelled due to lab abnl)
- Admitted 8/23/16, seen 9/15, readmitted 9/23 had BiV, readmitted 10/31, discharged and presented at an outside hospital 2 days later and transferred to local hospital
- 11/16 my introduction to her
- 12/16
- .......
Integrated Systems Response to Systolic Dysfunction

**Initiator**
- Insult to LV function (eg, MI, myocarditis)

**Acute Adaptation**
- Neurohormonal Activation (SNS, RAAS, AVP)
  - ↓ CO
  - ↓ BP
  - Enhanced renal Na+ and volume retention: ↑ Preload volume (Frank-Starling)
  - Tachycardia, vasoconstriction, ↑ contractility,

- Preserve CO and systemic pressures
Excitation-Contraction Coupling in HF

Ca\textsuperscript{2+} entry

Ca\textsuperscript{2+} exit

Ca\textsuperscript{2+} entry

RyR

SERCA

75%

25%

1%

75%

25%

3Na\textsuperscript{+}

Contraction cycle

Bers & Borlaug  Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine, 11th Ed

CHF
Abnormalities in β-AR Density and Coupling

**Diagram Content:****
- **Metabolism:** Glycolysis, Lipolysis, Citrate cycle, ADP+Pi, ATP, Myosin ATPase, ATP, ADP+Pi, Troponin C, cAMP via Trl, cAMP via PLB.
- **β-Adrenergic agonist:** GTP, Adenyl cyclase, AKAP, Ca²⁺, SR, P, PLB, PKA.
- **Myocardial mechanics:** Contractility, lusitropy, Stroke volume, Cardiac output.
- **Myocardial metabolism:** Glycolysis, O₂ uptake ↑ ATP, GPCR, activates cAMP and PKA.
- **Signal systems:** GPCR, can activate PKC and MAPK.
- **Coronary arterioles:** Constriction, + Direct dilation, +++ indirect dilation (metabolic).
- **Peripheral arterioles:** Constriction, SVR ↑, SBP ↑, + Dilation, SVR ↓, SBP ↓.

**Table Content:****

<table>
<thead>
<tr>
<th></th>
<th>ALPHA₂ MEDIATED</th>
<th>BETA MEDIATED</th>
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<tbody>
<tr>
<td>Electrophysiologic effects</td>
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<tr>
<td>Conduction</td>
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<tr>
<td>Pacemaker</td>
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<td>Heart rate</td>
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<td>AP duration</td>
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<tr>
<td>Myocardial mechanics</td>
<td>±</td>
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<tr>
<td>Contractility, lusitropy</td>
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<tr>
<td>Stroke volume</td>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Myocardial metabolism</td>
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<td>±</td>
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<tr>
<td>Glycolysis</td>
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</tr>
<tr>
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<td></td>
<td>+++ indirect dilation (metabolic)</td>
</tr>
<tr>
<td>SVR ↑</td>
<td></td>
<td></td>
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<tr>
<td>SBP ↑</td>
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</tbody>
</table>
Chronic NH Hyper-Activation and LV Overfilling Lead to Eccentric LV Remodeling

Laplace’s Law: Wall stress $\sim P \cdot \frac{r}{2h}$

- ↑wall stress, ↑$O_2$ demand
- ↓pump efficiency, ↑mitral insufficiency, dyssynchrony

Normal

Systolic Heart Failure
# Neurohormonal Derangements

<table>
<thead>
<tr>
<th>Pro-Remodeling</th>
<th>Anti-Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (NE)</td>
<td>Natriuretic peptides (NP)</td>
</tr>
<tr>
<td>Angiotensin II (Ang II)</td>
<td>Nitric Oxide (NO)</td>
</tr>
<tr>
<td>Aldosterone (aldo)</td>
<td>Prostacyclin (PGI₂)</td>
</tr>
<tr>
<td>Endothelin (ET)</td>
<td></td>
</tr>
<tr>
<td>Vasopressin (AVP)</td>
<td></td>
</tr>
<tr>
<td><strong>Stimulate hypertrophy, remodeling, fibrosis, apoptosis, fetal gene expression, contractile abnormalities</strong></td>
<td><strong>Anti-hypertrophic</strong></td>
</tr>
<tr>
<td><strong>Lead to vasoconstriction, sodium and fluid retention, endothelial dysfunction</strong></td>
<td><strong>Anti-proliferative</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Vasodilatory</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Relax ventricular loading Conditions, promote Diuresis, anti-remodeling, Enhance endothelium</strong></td>
</tr>
<tr>
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</tr>
</tbody>
</table>
LV Pressure-Volume Loop

- LV Pressure
- LV Volume
- ESV
- EDV ("preload")
- SV
- SBP
- EDP
LV Pressure-Volume Loop

ESPVR ("contractility")
LV Pressure-Volume Loop

ESPVR ("contractility")

EDPVR ("passive stiffness")
The Failing Heart is More Afterload-Sensitive than the Normal LV

Vasoconstriction

LV Pressure

LV Volume

Normal

Systolic HF
The Failing Heart is More Afterload-Sensitive than the Normal LV

LV Pressure

Vasoconstriction
Vasodilation

Normal

LV Volume

Systolic HF
The Failing Heart is More Afterload-Sensitive than the Normal LV

LV Pressure

LV Volume

Normal

Systolic HF

Vasoconstriction

Vasodilation
Hemodynamic Derangements in HFrEF: A Progression

- Normal
- Stage B HF (ASLVD) NYHA II-III
- Stage C HF NYHA IV
- Stage D HF NYHA IV

LV Pressure: SV → SV → SV → SV
SBP: ↓ ↓ ↓
LVEDP: ↑ ↑ ↑
EDV: ↑ ↑ ↑
LV Volume: ↑ ↑ ↑
“Flat” Starling Curve: ↓ LV preload-sensitivity in HFrEF

- Normal
- Systolic HF

LV Stroke Work

PCWP or LVDP
“Flat” Starling Curve: ↓ LV preload-sensitivity in HFrEF
“Flat” Starling Curve: ↓ LV preload-sensitivity in HFrEF
Enhanced Diastolic Ventricular Interaction in Advanced HFrEF
PCWP 32 mmHg

RAP 30 mmHg

Diuretic

PCWP 27 mmHg

RAP 18 mmHg

LV transmural FP = PCW – RA = 2 mmHg

LV transmural FP = PCW – RA = 9 mmHg
Ventricular interdependence in right heart failure from group 2 PH. A, typical equalization in RAP and PCWP from enhanced interdependence in a patient with biventricular HF, group 2 PH, and severe functional tricuspid insufficiency.

Marco Guazzi, and Barry A. Borlaug Circulation. 2012;126:975-990

Copyright © American Heart Association, Inc. All rights reserved.
Diagram showing the various hemodynamic stages observed in group 2 PH. A, Passive.
Pulmonary artery systolic pressure (PASP) estimates are a risk factor for death.

Marco Guazzi, and Barry A. Borlaug Circulation. 2012;126:975-990
Extracardiac Sequelae

- Hepatic Congestion/dysfunction/ascites
- Anemia/iron deficiency
- Endothelial Dysfunction
- Oxidative Stress
- Sleep disordered breathing
Fig. 1. Pathophysiological mechanisms of CRS.
Renal Dysfunction in HF

Heywood J Card Fail, 2005

Tang & Mullens Heart 2010
Consensus Conference of Acute Dialysis Quality Initiative Group
classification of cardiorenal syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Acute worsening heart function</td>
<td>Kidney injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 2</td>
<td>Chronic abnormalities in heart function</td>
<td>Kidney injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 3</td>
<td>Acute worsening of kidney function or AKI</td>
<td>Heart injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 4</td>
<td>CKD</td>
<td>Heart injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 5</td>
<td>Systemic conditions</td>
<td>Simultaneous injury and/or dysfunction of heart and kidney</td>
</tr>
</tbody>
</table>
Alterations in Skeletal Muscle

Skeletal Muscle Δ in HF

Fiber type

1, lia

lib

Krebs cycle

Ox Phos

Lipid oxidation

Capillary density

Mitochondria

Decreased activity
Decreased perfusion

Muscle wasting
fatigue

Decreased
aerobic capacity

Respiratory
muscle changes

Catabolic factors
Insulin resistance

Left ventricular
dysfunction

Increased
vascular
resistance

Sympathetic
activation

Baroreflex
downregulation

Ergoreflex
activation

Increased
VE/VO2

Fatigue

Breathlessness
**HF = A Systemic Inflammatory Disease**

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers (n=14)</th>
<th>CHF no oedema (n=20)</th>
<th>CHF oedema (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin (EU/mL)</td>
<td>0.46 (0.21)</td>
<td>0.37 (0.23)</td>
<td>0.74 (0.45)</td>
</tr>
<tr>
<td>LBP (g/mL)</td>
<td>9.6 (4.9)</td>
<td>10.4 (5.3)</td>
<td>12.1 (6.0)</td>
</tr>
<tr>
<td>Lipopolysaccharide/ log LBP ratio</td>
<td>0.54 (0.20)</td>
<td>0.44 (0.30)</td>
<td>0.75 (0.49)</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>24.6 (8.9)</td>
<td>25.8 (7.9)</td>
<td>36.6 (12.3)</td>
</tr>
<tr>
<td>Soluble TNF receptor-1 (pg/mL)</td>
<td>708 (213)</td>
<td>1077 (529)</td>
<td>1922 (1399)</td>
</tr>
<tr>
<td>Soluble TNF receptor-2 (pg/mL)</td>
<td>1465 (835)</td>
<td>2096 (1360)</td>
<td>3143 (1690)</td>
</tr>
<tr>
<td>Soluble CD14 (ng/mL)</td>
<td>3456 (583)</td>
<td>3674 (454)</td>
<td>4243 (688)</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>87 (16)</td>
<td>106 (73)</td>
<td>145 (94)</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>2.0 (0.4)</td>
<td>4.3 (5.5)</td>
<td>14.7 (17.3)</td>
</tr>
<tr>
<td>C-reactive (mg/L)</td>
<td>5.6 (1.7)</td>
<td>9.5 (9.5)</td>
<td>19.7 (17.1)</td>
</tr>
</tbody>
</table>

Nebauer: *Lancet*, 1999

Untoward effects of inflammatory mediators in heart failure

- Left-ventricular dysfunction
- Pulmonary oedema
- Cardiomyopathy
- Reduced blood flow in leg
- Left-ventricular remodeling
- β-receptor uncoupling from adenylate cyclase
- Activation of the fetal gene programme
- Alterations of the extracellular matrix


Mann: *Lancet*, 1999
Diagram indicating 2 x 2 table of hemodynamic profiles for patients presenting with heart failure. Most patients can be classified in a 2-minute bedside assessment according to the signs and symptoms shown although in practice some patients may be on the border between the warm-and-wet and cold-and-wet profiles. This classification helps guide initial therapy and prognosis for patients presenting with advanced heart failure. Although most patients presenting with hypoperfusion also have elevated filling pressures (cold and wet profile), many patients present with elevated filling pressures without major reduction in perfusion (warm and wet profile). Patients presenting with symptoms of heart failure at rest or minimal exertion without clinical evidence of elevated filling pressures or hypoperfusion (warm and dry profile) should be carefully evaluated to determine whether their symptoms result from heart failure. Reprinted with permission from Dr Stevenson.
**FIGURE 1** Biomarkers Indications for Use

Colors correspond to COR in Table 1.

*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.
# Causes of Elevated Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Selected Potential Causes of Elevated Natriuretic Peptide Levels (38-41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
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<tr>
<td>HF, including RV syndromes</td>
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<tr>
<td>Acute coronary syndromes</td>
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<td>Heart muscle disease, including LVH</td>
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<td>Valvular heart disease</td>
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<td>Pericardial disease</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>Myocarditis</td>
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<td>Cardiac surgery</td>
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<td>Cardioversion</td>
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<tr>
<td>Toxic-metabolic myocardial insults, including cancer chemotherapy</td>
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<tr>
<td><strong>Noncardiac</strong></td>
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<tr>
<td>Advancing age</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Renal failure</td>
<td></td>
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<tr>
<td>Pulmonary: obstructive sleep apnea, severe pneumonia</td>
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<tr>
<td>Pulmonary hypertension</td>
<td></td>
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<tr>
<td>Critical illness</td>
<td></td>
</tr>
<tr>
<td>Bacterial sepsis</td>
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<tr>
<td>Severe burns</td>
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</tr>
</tbody>
</table>

Modified from Table 8 of the 2013 HF guideline (9). HF indicates heart failure; LVH, left ventricular hypertrophy; and RV, right ventricular.
ACC/AHA/HFSA focused updated guidelines for HF

**FIGURE 2** Treatment of HFrEF Stage C and D

- **Step 1**: Establish Dx of HFrEF; assess volume; initiate GDMT
- **Step 2**: Consider the following patient scenarios
  - NYHA class II–IV, provided est. CrCl ≥30 mL/min & K+ ≤5.0 mEq/L
    - Aldosterone antagonist (COR I)
  - NYHA class II–III HF
    - Adequate BP on ACEI or ARB; No C/I to ARB or sacubitril
      - Discontinue ACEI or ARB; initiate ARNI* (COR I)
  - NYHA class III–IV, in black patients
    - Hydral-Nitrates†† (COR I)
  - NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
    - ICD‡ (COR I)
  - NYHA class II–IV, LVEF ≤35%; NSR & QRS ≥150 ms with LBBB pattern
    - CRT or CRT-D‡ (COR I)
  - NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
    - Ivabradine (COR IIb)

**Step 3**: Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

- **Step 4**: Reassess symptoms
  - Paliative care† (COR I)
  - Transplant‡ (COR I)
  - Refractory NYHA class III–IV (Stage D)
  - LVAD‡ (COR IIa)
  - Symptoms improved
  - Investigational studies§

**Step 5**: Consider additional therapy

Colors correspond to COR in Table 1. For all medical therapies, dosing should be optimized and serial assessment exercised.

*See text for important treatment directions.
†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; LBBB, left bundle branch block; LVAD, left ventricular assist device; NYHA, New York Heart Association.
Advanced HF is the presence of progressive and/or persistent severe symptoms of heart failure despite optimized medical, surgical and device therapy.

Fig. 1. Classification schemes for heart failure severity. Overlapping classification systems provide complementary descriptive and prognostic information for patients with advanced heart disease. NYHA classifies dynamic functional limitation, the American Heart Association/American College of Cardiology-Stages of Heart Failure highlight antecedent risk factors and disease progression, while the INTERMACS patient profiles integrate symptom burden and ongoing measures use to treat evolving shock.
### Patient Profile Official Shorthand

1. "Crash and burn"

2. "Sliding fast" on inotropes

3. "Stable" on continuous inotropes

4. Resting symptoms on oral therapy at home

5. "Housebound", comfortable at rest but symptoms with minimum activities of daily living

6. "Walking wounded", activities of daily living possible by meaningful activity limited

7. Advanced NYHA class III

---

Definition of Advanced Heart Failure

1. Moderate to severe symptoms of dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention and/or reduced cardiac output
3. Objective evidence of severe cardiac dysfunction demonstrated by at least 1 of the following:
   1. Left ventricular ejection fraction <30%
   2. Pseudonormal or restrictive mitral inflow pattern by Doppler
   3. High left and/or right ventricular filling pressures, or
   4. Elevated B-type natriuretic peptide
4. Severe impairment of functional capacity as demonstrated by either inability to exercise, 6-min walk distance <300 m, or peak oxygen uptake <12 to 14 mL · g⁻¹ · min⁻¹
5. History of at least 1 hospitalization in the past 6 mo
6. Characteristics should be present despite optimal medical therapy
# Definition of Advanced HF Across Cardiovascular Societies

<table>
<thead>
<tr>
<th>Severe Symptoms</th>
<th>Multiple Hospitalizations</th>
<th>Optimal Therapy</th>
<th>Inotropic Support</th>
<th>Fluid Retention and/or Peripheral Hypoperfusion</th>
<th>Severe Functional Capacity Impairment†</th>
<th>Reduced Ejection Fraction</th>
<th>Doppler Echo†</th>
<th>Hemodynamics§</th>
<th>Elevated Natriuretic Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA</td>
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<td>x</td>
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<td>HFSA</td>
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<td>ESC</td>
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<table>
<thead>
<tr>
<th>Refractory symptoms</th>
<th>Exercise Intolerance</th>
<th>Objective evidence of severe cardiac dysfunction</th>
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<tbody>
<tr>
<td>Severe Symptoms</td>
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<td>Hemodynamics§</td>
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<tr>
<td>Elevated Natriuretic Peptides</td>
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</tbody>
</table>
A depiction of the clinical course of heart failure with associated types and intensities of available therapies.

Onset of CHF → Sudden Death → Decompensations → Pump Failure

Traditional Care
Including disease-modifying therapies

Palliative Care
Including symptom management

Transition to Advanced Heart Failure:
- Oral therapies failing
- A time for many major decisions
- Consider MCS and/or transplantation, if eligible
- Consider inversion of care plan to one dominated by a palliative approach, which may involve formal hospice
Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.
Impact of recurrent heart failure hospitalization on mortality. Median survival (50% mortality) with 95% confidence limits in patients with heart failure after each heart failure hospitalization. (From Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154(2):262;)

Figure 2

Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.
Who Has Advanced Heart Failure? Definition and Epidemiology

![Pie charts showing causes of death in HF patients in the community and causes of all hospitalizations after HF diagnosis in the community.]

Congestive Heart Failure
Prognosis is not only about expectations for survival.


Costs/Burden
Direct Medical Costs
Indirect Costs
Lost Opportunities
Caregiver Burden

Outcomes Relevant to an Individual Patient

Survival

Quality of Life
Symptoms
Physical Function
Mental
Emotional
Social
Our study suggests that the number of HF hospitalizations may serve as an integrated measure of severity over time. Throughout the progression of HF, many decisions need to be individualized in light of all available information. The number of hospitalizations does not replace consideration of multiple factors such as age, cardiac and renal function, functional status, and comorbidities. However, the current study suggests that the number of HF hospitalizations may be useful to triage patients for the therapies that benefit most at different stages of the disease. Perhaps most importantly, repeated rehospitalizations for HF should trigger individualized discussion with the patient and family about the goals of care for the limited time remaining.
## Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>High admission blood pressure is associated with lower mortality postdischarge. Readmission rate: 30% at 90 d for both normotensive and hypertensive patients</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>Associated with 2-fold increase in postdischarge mortality compared with patients with primary cardiomyopathy. In CHD patients there is an increased post discharge mortality in response to short term intravenous milrinone compared with placebo.</td>
</tr>
<tr>
<td><strong>Troponin release</strong></td>
<td>30–70% of patients hospitalized with AHFS have detectable plasma levels of cardiac troponin. Associated with a 2-fold increase in post discharge mortality and a 3-fold increase in rehospitalization.</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>BUN and BUN/creatinine ratio appear to be better prognostic indicators than creatinine. Relatively minor increase in BUN is associated with 2- to 3-fold increase in postdischarge mortality.</td>
</tr>
<tr>
<td><strong>Hyponatremia</strong></td>
<td>25% of patients with AHFS have mild hyponatremia, associated with a 2-3 fold increase in in-hospitality and post discharge mortality.</td>
</tr>
<tr>
<td><strong>Natriuretic peptides</strong></td>
<td>Levels correlate weakly with elevated LV filling pressures. Increased levels are associated with higher postdischarge mortality and repeated hospitalizations.</td>
</tr>
<tr>
<td><strong>PCWP</strong></td>
<td>Reduction in PCWP during hospitalization, but not an increase in the cardiac output, has been associated with improved postdischarge survival. Reduction in PCWP with agents such as milrinone and dobutamine is associated with worse outcomes.</td>
</tr>
<tr>
<td><strong>Functional capacity</strong></td>
<td>6-minute walk test is emerging as an important predictor of postdischarge outcomes.</td>
</tr>
<tr>
<td><strong>Other prognostic factors</strong></td>
<td>LVEF, anemia, diabetes mellitus, new sustained arrhythmias, and nonuse of neurohormonal antagonists.</td>
</tr>
</tbody>
</table>
Precipitants for Decompensated Heart failure

Nonadherence
  - Medication noncompliance
  - Dietary indiscretion

Arrhythmias
  - Atrial fibrillation/atrial flutter
  - Ventricular tachycardia

Infection

Ischemia

Valvular disease
  - Mitral regurgitation
  - Aortic stenosis

Thyroid disease

Renal failure

Anemia

Medications: TZD’s, NSAIDs, prednisone, CCB’s, antiarrhythmics

Substance abuse/use cocaine, ETOH

PE/COPD exacerbation/uncontrolled HTN/Overaggressive BB titration
Tailored Therapy in Advanced Heart Failure

Fig. 1. Dyadic relationship between patient and HF team to engage in shared decision making and monitoring to inform advanced therapy options.
Heart failure medical trials enrolling New York Heart Association class III–IV patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>NYHA Class</th>
<th>Drug</th>
<th>Mortality Relative Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>IV</td>
<td>Enalapril</td>
<td>31</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>III-IV</td>
<td>Bisoprolol</td>
<td>34</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>IV</td>
<td>Carvedilol</td>
<td>35</td>
</tr>
<tr>
<td>RALES</td>
<td>III-IV</td>
<td>Spironolactone</td>
<td>30</td>
</tr>
<tr>
<td>A-HeFT</td>
<td>III-IV</td>
<td>ISDN/Hydralazine</td>
<td>43</td>
</tr>
</tbody>
</table>
Fig. 1. Cardiac implanted electronic device algorithm in management of heart failure with reduced ejection fraction. Initial evaluation starts with identification of patients who benefit from implantable cardioverter defibrillator (ICD) for primary prevention. These patients should be on optimal medical therapy as part of their treatment strategy. A waiting period of 40 days applies for patients who have a reduced ejection fraction as a result of a myocardial infarction before they qualify for an ICD. Patients with wide QRS duration should be considered for a cardiac resynchronization therapy (CRT). LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
Fig. 4. Remote monitoring strategies for heart failure care. Home monitoring systems for implanted cardiac electrical devices provide remote transmission of rhythm analysis, baseline electrocardiograph, transthoracic impedance, and patient activity. Commercially available devices at home can provide patient data to upload to the Internet or can be web-connected directly. The flow of information can feed into a multidisciplinary heart failure clinic and can provide the opportunity to make adjustments to home medications (ie, beta-blockers or diuretics) or prompt a request for the patient to seek unscheduled medical evaluation. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
Suggested hemodynamic goals in advanced HF

- Goal Hemodynamic Parameter
- Maintain blood pressure: SBP 80–90 mm Hg, MAP 65 mm Hg
- Decrease right-sided filling pressures: CVP <8 mm Hg
- Decrease left-sided filling pressures: PCW <16 mm Hg
- Decrease peripheral resistance: SVR 1000–1200 dyne/s/cm²
- Decrease pulmonary resistance: Mean PA 25% reduction, PVR <3 WU, TPG <15 mm Hg
- Increase cardiac output: Cardiac index 2.2 L/min/m²
### Selected Prognostic Models in Heart failure

<table>
<thead>
<tr>
<th>Model</th>
<th>Key Covariates</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure Survival Score23</td>
<td>Peak Vo₂, LVEF, serum sodium, mean BP, HR, ischemic etiology, QRS duration/morphology</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Seattle Heart Failure Model22 (depts.washington.edu/shfm)²²a</td>
<td>NYHA function class, ischemic etiology, diuretic dose, LVEF, SBP, sodium, hemoglobin, percent lymphocytes, uric acid, and cholesterol</td>
<td>All-cause mortality, urgent transplantation, or LVAD implantation</td>
</tr>
<tr>
<td><strong>Hospitalized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVEREST Risk Model22</td>
<td>Age, diabetes, h/o stroke, h/o arrhythmia, β-blocker use, BUN, sodium, BNP, KCCQ scores</td>
<td>The combined end point of mortality or persistently poor quality of life (KCCQ &lt;45) over the 6 mo after discharge</td>
</tr>
<tr>
<td>EFFECT29</td>
<td>Age, SBP, respiratory rate, sodium, hemoglobin, BUN, h/o CVA, h/o dementia, h/o COPD, h/o cirrhosis, h/o cancer</td>
<td>30-d and 1-y mortality</td>
</tr>
<tr>
<td>ADHERE28</td>
<td>BUN, SBP, serum creatinine</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>ESCAPE Discharge Score31</td>
<td>BNP, cardiopulmonary resuscitation or mechanical ventilation during hospitalization, BUN, sodium, age &gt;70 y, daily loop diuretic dose, lack of β-blocker, 6-min walk distance</td>
<td>6-mo mortality</td>
</tr>
</tbody>
</table>
### Triggers for Formally Assessing Prognosis and Having Conversations About Goals of Care and Voluntary Advance Care Planning

<table>
<thead>
<tr>
<th>Routine</th>
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</thead>
<tbody>
<tr>
<td>“Annual Heart Failure Review” with a scheduled clinic visit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event-driven “milestones” that should prompt reassessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased symptom burden and/or decreased quality of life</td>
</tr>
<tr>
<td>Significant decrease in functional capacity</td>
</tr>
<tr>
<td>- Loss of ADLs</td>
</tr>
<tr>
<td>- Falls</td>
</tr>
<tr>
<td>- Transition in living situation (independent to assisted or LTC)</td>
</tr>
<tr>
<td>Worsening heart failure prompting hospitalization, particularly if recurrent (57)</td>
</tr>
<tr>
<td>Serial increases of maintenance diuretic dose</td>
</tr>
<tr>
<td>Symptomatic hypotension, azotemia, or refractory fluid retention necessitating neurohormonal medication underdosing or withdrawal (58)</td>
</tr>
<tr>
<td>Circulatory-renal limitations to ACEI/ARB</td>
</tr>
<tr>
<td>Decrease or discontinuation of β-blockers because of hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other important comorbidities: new cancer, etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>First or recurrent ICD shock for VT/VF (59)</td>
</tr>
<tr>
<td>Initiation of intravenous inotropic support</td>
</tr>
<tr>
<td>Consideration of renal replacement therapy</td>
</tr>
<tr>
<td>Major “life events”: death of a spouse</td>
</tr>
</tbody>
</table>
Indicators of advanced heart failure that should trigger consideration of referral for evaluation of advanced therapies

- Need for intravenous inotropic therapy for symptomatic relief or to maintain end-organ function
- Peak VO2 <14 mL/kg/min or less than 50% predicted
- 6 minute walk distance less than 300 m
- 2 heart failure hospitalizations in 12 months
- Worsening right heart failure and secondary pulmonary hypertension
- Diuretic refractoriness associated with worsening renal function
- Circulatory-renal limitations to RAAS inhibition or beta-blocker therapy
- Progressive/persistent NYHA functional class III-IV symptoms
- Increased 1-year mortality (eg, >20%–25%) predicted by heart failure survival models
- Progressive renal or hepatic end-organ dysfunction
- Persistent hyponatremia (serum sodium <134 mEq/L)
- Cardiac cachexia
- Inability to perform activities of daily living

Abbreviations: NYHA, New York Heart Association; RAAS, renin angiotensin aldosterone system; VO2, oxygen uptake. Adapted from Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. Circulation 2012;125:1311; with permission.
HF clinic

- Disease Management Clinic
- Multidisciplinary team
- Work up of advanced HF patients
- CPET
- Amyloid clinic
- CardioMems
Figure 3 Compared with normal controls (A and B), the slope of the end-systolic pressure–volume relationship (end-systolic elastance; Ees, dotted lines) is increased in heart failure with preserved ejection fraction (HFrEF) (C and D). This leads to exaggerated increases and decreases in blood pressure for the same change in afterload (A and C) or preload (B and D) in HFrEF, accounting for the greater predilection for hypertensive crisis and/or hypotension and azotemia with over-diuresis or overly vigorous vasodilation.
Enhanced afterload sensitivity of the right ventricle compared with the left.

Marco Guazzi, and Barry A. Borlaug. Circulation. 2012;126:975-990