Heart Failure with Reduced EF

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Section of Heart Failure and Cardiac Transplantation
Disclosures

• No personal disclosures or relationships
Agenda

- Epidemiology
- Pathophysiology
- Diagnosis
- Treatment
Epidemiology of HF

- Survival similar to advanced non-small cell lung cancer...


T4 NSCLC (Stage 3B or worse)
The rising prevalence of HF

- HTN, diabetes, obesity epidemics on the rise
- Better treatment of heart attacks
- Effective but not curative Rx for HF
- Aging population

Source: NHANES (1999-2004), CDC/NCHS and the American Heart Association
Annual Incidence of HF

Prevalence and Incidence of HF Worldwide

- Incidence (%):
  - 0.1–0.2: Portugal, Spain, Germany, Sweden, Italy, UK, Netherlands, USA, China, Japan, India
  - 0.39–0.44: Portugal
  - 0.38:
  - 0.31–0.39:
  - 0.05–0.17:
  - 0.2:

- Prevalence (%):
  - 1–2: Portugal, Denmark, Sweden
  - 2.1: Spain
  - 1.6–1.8: Germany
  - 1.8–2.2: Sweden
  - 1.44: Italy
  - 1.5–1.9: Netherlands
  - 1.3: USA
  - 1:
  - 0.12–0.44: China
  - 6.7: Malaysia
  - 4.5: Singapore
  - 1:
  - 1–2: South America, Australia
## Heart Failure Categories

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Outcomes</th>
<th>Guideline-Directed Medical Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Older Age</td>
<td>Male Sex</td>
</tr>
<tr>
<td><strong>HFpEF</strong> (LVEF &gt; 50%)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>HFmrEF</strong> (LVEF 40-50%)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>HFrEF</strong> (LVEF &lt; 40%)</td>
<td>+</td>
<td>++++</td>
</tr>
</tbody>
</table>

Economic impact

- HF is the primary reason for 12-15 million office visits and 6.5 million hospital days annually.
- In patients ages ≥65 years, the 30-day hospital readmission rate is approximately 30%
- HF represents America’s largest diagnosis-related group, and the 90-day readmission rate after an index hospitalization for HF is as high as 47% of discharges, leading to the fact that more Medicare dollars are spent on HF than on any other diagnosis
- over one-half of the admissions are thought to be potentially preventable (improve quality not only quantity of admission for HF, optimize GDMT, achieve euvoolemia, educate, 1 week f/u post d/c)
## Risk factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Framingham Heart Study</th>
<th>Cardiovascular Health Study</th>
<th>NHANES Epidemiology Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Prevalence</td>
<td>PAR</td>
</tr>
<tr>
<td>Hypertension</td>
<td>M 2.1</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>M 6.3</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Angina</td>
<td>M 1.4</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>M 1.8</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy (EKG)</td>
<td>M 2.2</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>M 2.5</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atrial Fibrillation (EKG)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low Physical Activity</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overweight</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&lt;High School Education</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- CAD present in >60% of patients with HFREF
Physiology

- Excitation-contraction coupling is the mechanism by which small amounts of extracellular calcium enter the myocyte to initiate myocardial contraction. Myocardial relaxation is an ATP-dependent process, unlike myocardial contraction.
- Calcium-mediated calcium release triggered by this extracellular calcium leads to release of large concentrations of calcium from the SR that bind to troponin C. This process does not require ATP, as the calcium flows down a concentration gradient from the SR into the cytoplasm.
- All of the calcium released into the cytoplasm must be removed in order for the myocardium to relax. This process is mediated by the SR calcium ATPase (SERCA2a). SERCA2a function requires ATP, as calcium must flow against a significant concentration gradient.
- Phospholamban is a regulatory protein that binds and inhibits the activity of SERCA2a, limiting calcium entry into the SR.
- SERCA is GOOD and phospholamban should be phosphorylated to prevent inhibition of SERCA.
Pressure-Volume loops

The Frank-Starling Relationship

RV vs LV PV Loops
Effects of Different Interventions on Pressure-Volume Loops

B-blocker

Dobutamine

Isoproterenol

Phenylephrine

Nitroprusside

IV fluids

Green=post-intervention
Pathophysiology (SNS)

• The earliest response to decreased cardiac output is activation of the sympathetic nervous system.
• The heart predominantly expresses beta-1 and beta-2 adrenergic receptors in a 70:30 ratio. Beta-1 receptors are coupled with Gs proteins, whereas beta-2 receptors are coupled with Gs and Gi proteins.
• Activation of Gs proteins results in up-regulation of adenylate cyclase activity, which increases c AMP, which increases protein kinase A, which causes positive inotropy, positive lusitropy.
• Alpha-adrenergic 1 receptors located in major arteries, when stimulated they cause vasoconstriction by Gq proteins. A2 are in the brain and when stimulated cause hypotension.
Pathophysicsiology (RAAS)

• Renin is released from juxtaglomerular cells in the afferent arteriole of the nephron in response to decreased renal perfusion and SNS activation.

• Angiotensin II is a vasoconstrictor causing increased afterload, hypertrophy, apoptosis, aldosterone upregulation, sodium reabsorption, SNS activation
Pathophysiology (Natriuretic peptides)

- Atrial natriuretic peptide (ANP), and B-type natriuretic peptide (BNP) are released from cardiomyocytes in response to increased atrial and ventricular wall stress and bind NPR (ANP=10XBNP affinity)
- The pro-protein proBNP is cleaved into BNP and the physiologically inactive molecule NT-proBNP. Natriuretic peptides are degraded by neprilysin, a neutral endopeptidase (NT-proBNP<<BNP).
- The natriuretic peptides have physiologic functions (via c GMP) that counter the effect of sustained SNS and RAAS activation.
# Neurohormones Involved in Ventricular Remodeling

<table>
<thead>
<tr>
<th>Neurohormone</th>
<th>Adaptive Responses</th>
<th>Maladaptive Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Increased heart rate, increased contractility</td>
<td>Increased MVO₂, hypertrophy, myocyte apoptosis, arrhythmias</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Peripheral vasoconstriction, sodium reabsorption (proximal tubule)</td>
<td>Activation of the fetal gene program, myocardial fibrosis</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Sodium reabsorption (distal tubule)</td>
<td>Myocardial fibrosis</td>
</tr>
<tr>
<td>Arginine-vasopressin</td>
<td>Free water reabsorption</td>
<td>Peripheral vasoconstriction, decreased contractility</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td></td>
<td>Peripheral vasoconstriction</td>
</tr>
</tbody>
</table>
Ventricular Remodelling

- Ventricular remodeling begins with hypertrophy in response to increased wall stress, to decrease myocardial VO2 consumption.
- LV hypertrophy is associated with reactivation of fetal genes that alter the composition of contractile proteins in the myocardium. Adult isoforms of myosin with high ATPase activity are replaced with fetal low ATPase myosin, decreasing the ATP cost of wall tension generation.

\[ T = P \times \frac{r}{wt} \]
Diagnosis

- Increased filling pressures → Highest sensitivity: Orthopnea, PND, JVD > 12 cm, HJR, S3
- Low output → nausea, abd pain, fatigue, confusion, low PP
- BNP (careful in obese, elderly)
- TTE, evaluation for CAD
- Cardiac MRI in newly diagnosed patients with cardiomyopathy
- CPEx for risk stratification in symptomatic outpts
- RHC for pts with worsening symptoms and uncertain volume/cardiac output
ACC/AHA Staging of CHF

At Risk for Heart Failure

STAGE A 22%
- At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes
  - Obesity
  - Metabolic syndrome
- Patients:
  - Using diuretics
  - With HFxCM

STAGE B 34%
- Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

Development of symptoms of HF

Heart Failure

STAGE C 11%
- Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Known structural heart disease
  - Shortness of breath and fatigue, reduced exercise tolerance

STAGE D
- Refractory HF requiring specialized interventions
- e.g., Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

THERAPY GOALS
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

DRUGS
- ACEI or ARB in appropriate patients (see text)
- Beta-blockers in appropriate patients (see text)

DEVICES IN SELECTED PATIENTS
- Implantable defibrillators

THERAPY GOALS
- All measures under Stage A

DRUGS
- ACEI or ARB in appropriate patients (see text)
- Beta-blockers in appropriate patients (see text)

THERAPY GOALS
- All measures under Stages A and B
- Dietary salt restriction

DRUGS FOR ROUTINE USE
- Diuretics for fluid retention
- ACEI
- Beta-blockers

DEVICES IN SELECTED PATIENTS
- Bi-ventricular pacing
- Implantable defibrillators

THERAPY GOALS
- All measures under Stages A, B, C
- Decision re: appropriate level of care

OPTIONS
- Compassionate end-of-life care/hospice
- Extraordinary measures
- Heart transplant
- Chronic Inotropes
- Permanent mechanical support
- Experimental surgery or drugs
### Framingham Criteria for Diagnosing CHF

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Major or Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>PND or Orthopnea</td>
<td>Ankle edema</td>
<td>&gt; 4.5 kg weight loss in 5 days in response to therapy</td>
</tr>
<tr>
<td>Neck vein distension</td>
<td>Nocturnal cough</td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>Exertional dyspnea</td>
<td></td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Pleural effusion</td>
<td></td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>Vital Capacity decreased</td>
<td></td>
</tr>
<tr>
<td>S3 gallop</td>
<td>1/3 from maximum</td>
<td></td>
</tr>
<tr>
<td>CVP &gt; 16 cmH20</td>
<td>Tachycardia &gt; 120 bpm</td>
<td></td>
</tr>
<tr>
<td>Circulation time &gt; 25 seconds</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definite HF=2 major or 1 major+2 minor criteria
Practical Tips When Assessing the Jugular Venous Pressure (JVP)

1. Always start by assessing the patient sitting upright to exclude a very high JVP (which may be more difficult to detect when the patient is at a lower angle).

2. Inspect both sides of the patient’s neck.

3. The external jugular vein can be used to estimate the JVP especially when the internal jugular veins are not visible. Confirm a respirophasic component in external jugular veins before accepting it as a measure of the JVP.

4. Assess the patient at various angles off the horizontal (e.g., supine, 30 or 45 degrees off the horizontal, sitting, or standing) until the jugular venous pulsation is visible half-way up the neck.

5. If the JVP does not appear elevated when supine, press on the patient’s abdomen or right upper quadrant to see if the abdominojugular response is present.

6. To distinguish the carotid from the jugular venous impulse, apply pressure with your finger 1-2 inches below the impulse. If the pulsation disappears, it was the jugular vein; if the pulsation persists, it was the carotid artery.

7. Add 5cm if pt at 0 degrees, 8 cm at 30, 10 cm at 45

1 cm water = 0.74 mmHg

- In 20-30% JVD and PCW are discordant
- In COPD, ILD RA may be disproportionally elevated compared with LVEDP
- In MI JVD may be normal
- Always use more than one physical exam findings to increase sensitivity and combine them with Biomarkers and TTE/RHC parameters
Two-Minute Assessment of Hemodynamic Profiles

Evidence for Congestion (Elevated Filling Pressure)
- Orthopnea
- High Jugular Venous Pressure
- Increasing S₃
- Loud P₂
- Edema
- Ascites
- Rales (Uncommon)
- Abdominojugular Reflux
- Valsalva Square Wave

Evidence for Low Perfusion
- Narrow Pulse Pressure
- Pulsus Alteration
- Cool Forearms and Legs
- May Be Sleepy, Obtunded
- ACE Inhibitor-related Symptomatic Hypotension
- Declining Serum Sodium Level
- Worsening Renal Function

Congestion at Rest?
- No
  - Warm and Dry: A
  - Cold and Dry: L
- Yes
  - Warm and Wet: B
  - Cold and Wet: C
Biomarkers: Indications for Use

Prevention

- BNP or NT-proBNP (COR Iia)

Diagnosis

- BNP or NT-proBNP (COR I)
- BNP or NT-proBNP, and cardiac troponin (COR I)

Prognosis or added risk stratification

- Other biomarkers of myocardial injury or fibrosis* (COR IIb)
- Other biomarkers of myocardial injury or fibrosis* (COR IIb)
- Predischarge BNP or NT-proBNP (COR IIa)

<table>
<thead>
<tr>
<th>Non-cardiac</th>
<th>Rule out CHF (pg/ml)</th>
<th>Rule in CHF (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>NT-proBNP (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>50-75</td>
<td>300</td>
<td>900</td>
</tr>
<tr>
<td>75</td>
<td>300</td>
<td>1800</td>
</tr>
</tbody>
</table>

- Advanced age
- Ischaemic stroke
- Subarachnoid haemorrhage
- Renal dysfunction
- Liver dysfunction (mainly liver cirrhosis with ascites)
- Paraneoplastic syndrome
- Chronic obstructive pulmonary disease
- Severe infections (including pneumonia and sepsis)
- Severe burns
- Anaemia
- Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)
Non-invasive Hemodynamic Assessment

<table>
<thead>
<tr>
<th>HD Parameter</th>
<th>ECHO Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>IVC diameter and degree of change with sniff</td>
</tr>
<tr>
<td>RVSP</td>
<td>= PASP (if no pulmonic stenosis)</td>
</tr>
<tr>
<td></td>
<td>= 4 x (Peak TR Velocity)$^2$ + CVP</td>
</tr>
<tr>
<td>Mean PA pressure</td>
<td>= 79 – (0.45 x PA acceleration time)</td>
</tr>
<tr>
<td>PA end-diastolic pressure (PAEDP)</td>
<td>= 4 x (Velocity$_{endPR}$)$^2$ + CVP</td>
</tr>
<tr>
<td></td>
<td>(endPR = end of pulm regurgitation jet by continuous wave doppler)</td>
</tr>
<tr>
<td>PVR</td>
<td>= (TR velocity/VTI$_{IVOT}$) x 10 + 1.16</td>
</tr>
<tr>
<td>Left Atrial Pressure</td>
<td>(E/e' x 1.25) + 1.9</td>
</tr>
<tr>
<td></td>
<td>(E = early diastolic filling by mitral inflow PW, e' = TDI of lateral wall in apical 4 chamber view)</td>
</tr>
<tr>
<td>Stroke Volume</td>
<td>= Area$<em>{IVOT}$ x VTI$</em>{IVOT}$</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>= Stroke Volume x HR</td>
</tr>
<tr>
<td>SVR</td>
<td>= (MAP-CVP)/CO</td>
</tr>
<tr>
<td></td>
<td>= MR velocity/VTI$_{IVOT}$</td>
</tr>
</tbody>
</table>
Determining prognosis: Cardiopulmonary exercise testing

The NYHA classification is a subjective measure of functional capacity, and may be affected by symptoms due to noncardiovascular disease.
RHC: When to do?

• The ESCAPE trial demonstrated no significant benefit of routine RHC in patients with advanced heart failure.

• Currently, invasive RHC would be indicated for patients with:
  → decompensated heart failure who are not responding as expected (persistent symptoms, hypotension, renal failure despite apparent volume overload)

and

→ in patients in whom therapies with significant risks (inotropes, LVADs, transplant) are being considered.
Indications for Invasive Hemodynamic Monitoring in Heart Failure
From the 2013 ACCF/AHA Guideline for the Management of Heart Failure

1. Class I
Invasive hemodynamic monitoring should be performed to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment. (Level of Evidence: C)

2. Class IIa
Invasive hemodynamic monitoring can be useful for carefully selected patients with acute heart failure who have persistent symptoms despite empiric adjustment of standard therapies, and:
   A. whose fluid status, perfusion, or systemic or pulmonary vascular resistances are uncertain;
   B. whose systolic pressure remains low, or is associated with symptoms, despite initial therapy;
   C. whose renal function is worsening with therapy;
   D. who may require parenteral vasoactive agents; or
   E. who may need consideration for advanced device therapy or transplantation. (Level of Evidence: C)

3. Class III
("should not be performed since it is not helpful and may be harmful") Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated heart failure and congestion with symptomatic response to diuretics and vasodilators is not recommended. (Level of Evidence: B)
<table>
<thead>
<tr>
<th>Location</th>
<th>Average Normal Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium</td>
<td>5 mm Hg</td>
<td>2 – 8 mm Hg</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>25/5 mm Hg</td>
<td>(15-30)/(2-8) mm Hg</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>25/10 mm Hg (mean 15 mm Hg)</td>
<td>(15-30)/(4-12) mm Hg</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (PCWP)</td>
<td>9 mm Hg</td>
<td>4 – 12 mm Hg</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>100 dyne-s/cm$^5$</td>
<td>80 – 150 dyne-s/cm$^5$</td>
</tr>
<tr>
<td>Systemic vascular resistance (SVR)</td>
<td>1100 dyne-s/cm$^5$</td>
<td>800-1200 dyne-s/cm$^5$</td>
</tr>
</tbody>
</table>
Obtain accurate PCW

- Check saturation (>90%), check waveforms
- LVEDP can be >5mmHg higher in 30%, check it if unsure
Obtain accurate Cardiac Output

- Estimation, rather than measurement of VO$_2$, can lead to important errors when measuring cardiac output by the Fick method.

- Overall, the Fick method would be preferable in the setting of a low-output state as may occur in advanced heart failure; however, if VO$_2$ cannot be directly measured, than this advantage would be compromised, and it would be prudent to consider the cardiac output as assessed by both methods.

- When cardiac output is not low, and there is no significant tricuspid regurgitation, the thermodilution method will be at least as satisfactory as the Fick method.
CardioMEMS

An implantable sensor, which wirelessly transmits PA pressures, has gained FDA approval for New York Heart Association class III patients who have been hospitalized in the prior year. Benefit was demonstrated both in those with a reduced or preserved LVEF.
# Genetic screening

<table>
<thead>
<tr>
<th>Cardiomyopathy Phenotype</th>
<th>Gene Tests Available*</th>
<th>Yield of Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>MYH7, MYBPC3, TNNT2,</td>
<td>MYH7, MYBPC3 each</td>
</tr>
<tr>
<td></td>
<td>TNN3, TPM1, ACTC, MYL2,</td>
<td>account for 30%-40% of</td>
</tr>
<tr>
<td></td>
<td>MYL3.</td>
<td>mutations, TNNT2 for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10%-20%. Genetic cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>can be identified in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%-45% overall; up to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60%-65% when the family</td>
</tr>
<tr>
<td></td>
<td></td>
<td>history is positive.</td>
</tr>
<tr>
<td>DCM</td>
<td>LMNA, MYH7, TNNT2,</td>
<td>5.5%, 4.2%, 2.9%, for</td>
</tr>
<tr>
<td></td>
<td>SCN5A, DES, MYBPC3,</td>
<td>LMNA, MYH7, and TNNT2,</td>
</tr>
<tr>
<td></td>
<td>TNN3, TPM1, ACTC, PLN,</td>
<td>respectively. All data</td>
</tr>
<tr>
<td></td>
<td>LDB3 and TAZ.</td>
<td>are from research cohorts.</td>
</tr>
<tr>
<td>ARVD</td>
<td>DSP, PKP2, DSG2, DSC2</td>
<td>6%-16%, 11%-43%,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%-40%, for DSP, PKP2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and DSG2, respectively</td>
</tr>
<tr>
<td>LVNC</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>RCM</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiomyopathy Phenotype</th>
<th>Interval if genetic testing is negative and/or if clinical family screening is negative</th>
<th>Screening Interval if a mutation is present</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic</td>
<td>Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop</td>
<td>Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter.</td>
<td>B</td>
</tr>
<tr>
<td>Dilated</td>
<td>Every 3-5 years beginning in childhood</td>
<td>Yearly in childhood; every 1-3 years in adults.</td>
<td>B</td>
</tr>
<tr>
<td>ARVD/C</td>
<td>Every 3-5 years after age 10</td>
<td>Yearly after age 10 to 50 years of age.</td>
<td>C</td>
</tr>
<tr>
<td>LVNC</td>
<td>Every 3 years beginning in childhood</td>
<td>Yearly in childhood; every 1-3 years in adults.</td>
<td>C</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Every 3-5 years beginning in adulthood</td>
<td>Yearly in childhood; every 1-3 years in adults.</td>
<td>C</td>
</tr>
</tbody>
</table>
Disease Course

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
Treatment Goals

- Improve survival
- Improve symptoms, QOL
- Decrease readmissions
- Treat underlying conditions
# Treatment of Underlying Conditions

## Current Recommendations for the Surgical and Percutaneous Treatment of Coronary Artery Disease in Heart Failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG or percutaneous intervention is indicated for HFrEF or HFpEF patients on GDMT with angina and suitable coronary anatomy, especially for left main stenosis or left main equivalent</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF 35-50%) and significant multivessel CAD or proximal LAD stenosis when viable myocardium is present in the region of intended revascularization</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>CABG or medical therapy is reasonable to improve morbidity and mortality for patients with severe LV dysfunction (EF &lt;35%), HF, and significant CAD</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>CABG may be considered with the intent of improving survival in patients with ischemic heart disease, severe LV systolic dysfunction, and operable coronary anatomy whether or not viable myocardium is present</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>Surgical reverse remodeling or LV aneurysmectomy may be considered in HFrEF for specific indications, including intractable HF and ventricular arrhythmias</td>
<td>Iib</td>
<td>B</td>
</tr>
</tbody>
</table>
Step 1: Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2: Consider the following patient scenarios
- NYHA class II-IV, provided est. CCI >30 mL/min & K+>6.0 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
  - Hydralazine† (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 & LBBB ≥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 Iia)

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

Step 4: Reassess symptoms
- Refractory NYHA class III-IV (Stage D)
  - Symptoms improved
  - LVAD‡ (COR Ila)
  - Investigational studies§

Step 5: Consider additional therapy
- Palliative care‡ (COR I)
- Transplant‡ (COR I)

Continue GDMT with serial reassessment & optimized dosing/adherence

*CHANGING MEDICINE. CHANGING LIVES.*

UNIVERSITY OF IOWA HEALTH CARE
Medical Management: ACEi

- Pivotal trials: CONSENSUS, SOLVED Treatment, SOLVD Prevention
- Improve mortality, reduced adverse remodelling
- ATLAS trial: higher doses > lower doses
- Slight worsening of renal function, and slight increase in serum K levels are expected effects, and do not necessitate altering the therapeutic course
- If cough then switch to ARBs
Medical Management: B-blockers

• Trials: US Carvedilol trial followed by MERIT-HF, CIBIS-II for NYHA II-III, COPERNICUS and CAPRICORN for NYHA IV.

• Carvedilol, bisoprolol, metoprolol xl improve mortality and INCREASE LVEF, decrease MR, remodelling.
Medical Management: ARBs

- VAL-HEFT, CHARM-Alternative, CHARM-Added, VALIANT, ELITEII, OPTIMAAL, noninferiority to ARBs

- HEAAL: higher dose > lower dose

- ARBs should be prescribed in the event of ACEI intolerance due to cough or angioedema. ARBs do not provide any particular benefit over ACEIs if cardiorenal limitations (e.g., hypotension, renal insufficiency, hyperkalemia) are the reason for ACEI intolerance
Medical Management: Aldosterone antagonists

• Aldosterone antagonists should be considered in patients with symptomatic HF, as long as serum creatinine is <2.5 mg/dl and potassium levels are <5.0 mmol/L.

• 3 Trials: RALES, EPHESUS, EMPHASIS HF,
ARNI

Endogenous vasoactive peptides
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide, amyloid-β peptide)

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

Neprilysin inhibition

RAAS Activation

NEP inhibition alone not effective
ARNI

Magnitude of treatment benefit consistent in patients with and without ICD

- Cardiovascular death: Enalapril 16.5%, LCZ696 13.3% (↓20%)
- HF hospitalization: Enalapril 15.6%, LCZ696 12.8% (↓20%)
- Overall mortality: Enalapril 19.8%, LCZ696 17.0% (↓16%)
- HF death: Enalapril 4.4%, LCZ696 3.5% (↓21%) out of 331/1546 deaths (21.4%)
- Sudden death: Enalapril 7.4%, LCZ696 6.0% (↓20%) out of 561/1546 deaths (36.3%)

uihc.org
Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril: A Secondary Analysis of the PARADIGM-HF Trial

Alkay S. Desai, MD, MPH; Orly Vardany, PharmD; Brian Claggett, PhD; John J. V. McMurray, MD; Milton Parker, MD; Karl Swedberg, MD, PhD; Jean L. Rouleau, MD; Michael R. Zile, MD; Martin Lefkowitz, MD; Victor Shi, MD; Scott D. Solomon, MD

Serum potassium by study visit and treatment assignment in among MRA-treated subjects at baseline

Time to development of severe hyperkalemia (K>6.0) according to treatment assignment and MRA use as baseline
ARNI for Inpatients

- Recent data from the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) study suggest that the administration of an ARNI to patients stabilized after admission for acute decompensated HF may be safe and effective.
- It decreases BNP and improves secondary exploratory outcomes of HF hospitalization when started for inpatients on stable doses of diuretics off inotropes.
When to prescribe ARNI

• **Yes**
  NYHA II-III-IVa subjects tolerating ACE/ARB
  Subjects on low dose ACE/ARB
  ACE/ARB naïve subjects
  Hospitalized HF patients

• **Unknown**
  HF with Preserved EF
SGLT2 Antagonists

- provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2 (natriuresis, osmotic diureris)
- Improved outcomes in DAPA-HF regardless of diabetic status
- Don’t give if GFR<45
- Don’t give if DKA, recurrent UTI, foot ulceration, low bone density+falls
Ivabradine
When to prescribe Ivabradine

Indications:
• Symptomatic HFREF, LVEF<35%, in sinus rhythm with a resting heart rate ≥70 bpm, either on a maximum tolerated dose of a BB or have a contraindication to BB and are on ACEi/ARBs and MRA

Contraindications:
• Acute decompensated HF.
• BP< 90/60
• Atrial fibrillation
• Sick sinus syndrome, sinoatrial block or third degree AVB, unless a functioning demand pacemaker is present
• Severe hepatic impairment.
Medical Therapy: Hydralazine/Isosorbide Dinitrate

- Hydralazine and ISDN in combination should be considered, particularly in African-American populations, if advanced symptoms (e.g., HF of NYHA class III-IV) persist.
- H-ISDN-modest benefit vs placebo, inferior to ACE in V-HEFT I & II, benefit in AA in A-HEFT.
- Clinical adoption is low as 40-50% of pts don’t tolerate (headache, dizziness), poor adherence.
Digoxin:

- Digoxin may have symptomatic benefits in patients with HF, but effective serum levels rarely require doses >0.125 mg daily.
Antithrombotic treatment

- Anticoagulation with warfarin or a novel oral anticoagulant is warranted when HF is complicated by a history of a prior thromboembolic event (e.g., stroke), atrial fibrillation.
- Prefer warfarin for LV thrombus
Potentially harmful drugs to avoid

• NSAIDS
• TZD
• CCB
• Antiarrhythmics (except for amio, dofetilide)
• Careful with QTc prolonging drugs (Antibiotics, SSRIs, antiphychotics, hypoK/Mg, etc)
# Anemia in HF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/ Rationale</th>
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<tbody>
<tr>
<td>IIb: B-R</td>
<td></td>
<td>In patients with NYHA class II and III HF and iron deficiency (ferritin &lt;100 ng/mL or 100 to 300 ng/mL if transferrin saturation is &lt;20%), intravenous iron replacement might be reasonable to improve functional status and QoL.</td>
<td>NEW: New evidence consistent with therapeutic benefit.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.</td>
<td>NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.</td>
</tr>
</tbody>
</table>
Invasive treatment of secondary MR

LVEF 20-50%, LVESD<70mm on GDMT, CRT, NYHA II-Iva, not candidates for surgery, with secondary MR

+improvement in remodelling of the LV
-higher cost with TMVr

Stone GW, COAPT trial. NEJM 2018, In press
Chronic Disease Management Program

- Multidisciplinary HFDM programs reduce all-cause readmission rates by 20-30% and HF readmission rates by approximately 50%

- Favorable effects on mortality, quality of life, and cost of care have also been demonstrated in some but not all studies.
Chronic Disease Management Program

- Education and counseling
- Weight monitoring and self-adjustment of diuretic dosages (if appropriate);
- Behavioral strategies to promote adherence (e.g. pill boxes);
- Optimization of medical therapy, with titration of beta-blockers, renin-angiotensin system inhibitors, and other medications;
- Proactive management of signs and symptoms of worsening volume overload (e.g., adjustment of diuretic dosages);
- Assistance with social and financial concerns
- Vigilant follow-up, particularly during periods of transition (e.g., hospital to home);
- 24-hour access to providers via telephone.
Chronic Disease Management Program

Who to refer:

- Persistent New York Heart Association (NYHA) class II to IV symptoms, in spite of medical therapy
- Repetitive hospitalizations
- Multiple comorbid conditions (CKD, DM, COPD)
- History of nonadherence to diet, medications, and/or scheduled follow-up appointments
Conclusions

• Early recognition, evaluation and treatment of HF
• Do not underestimate findings of biomarkers and imaging
• Aggressive uptitration of medications, device therapies
• Non-invasive and invasive hemodynamic assessment
• Identify signs of stage D HF
Question 1

- A 55-year-old man with chronic heart failure (HF) with reduced ejection fraction is admitted with persistent dyspnea. During his hospitalization, his symptoms are refractory to increasing doses of diuretics. What’s next:

1. RHC
2. BNP
3. TTE
4. CPEX
Question 2

A 42-year-old male patient with EF of 35%. His medical regimen includes carvedilol 25 mg bid, lisinopril 10 mg daily, furosemide 20 mg daily when necessary. He currently has New York Heart Association (NYHA) class I symptoms, a normal physical examination, and blood pressure of 128/92 mm Hg. Which of the following is the next best step in management prior to evaluation for implantable cardioverter-defibrillator (ICD)?

1. Asa 81
2. Eplerenone 25
3. Increase lisinopril
4. Digoxin 0.125
Question 3

- A 55-year-old white woman with NICM, LVEF 32%, bp104/70 mm Hg, and pulse 72 bpm. Her jugular venous pressure is not elevated, normal S₁ and S₂ without murmurs or gallop, and there is no peripheral edema. Medications include lisinopril 5 mg daily, carvedilol 12.5 mg twice daily, and furosemide 40 mg twice daily. Her serum creatinine is 2.5 mg/dl.
- Which is the next most appropriate step in her care?
  1. Digoxin 0.125
  2. Increase coreg
  3. Add hydralazine/ISDN
  4. Decrease lisinopril
  5. Add spironolactone
Question 4

- A 69-year-old man with a history of prior myocardial with LVEF 30%. At discharge, his medications included atorvastatin 80 mg, aspirin 81 mg, lisinopril 40 mg, and carvedilol 25 mg twice daily. Laboratory values include stable creatinine of 1.4 mg/dl and potassium of 4.4 mEq/L. He underwent outpatient sleep study that was consistent with central sleep apnea (CSA).
- Which of the following therapies has been demonstrated to be of the greatest benefit in the treatment of this patient's CSA?
  1. CPAP
  2. Spironolactone
  3. Uvulectomy
  4. Oxygen at night
Question 5

- 62 yo AAM with HFREF, EF 30%, on metoprolol succinate 100 mg, lisinopril 20 mg, and furosemide 40 mg, NYHA III. K 4.8. What to do next:

1. Spironolactone
2. Hydral-IDN
3. Increase metoprolol
4. Increase lisinopril
Question 6

- 53 yo male ICM, HFREF 25%, NYHA IIIa, LBBB, QRS 165, GDMT, severe MR. What’s next:
  1. CRT
  2. MVR
  3. Transplant
  4. ARB