Update on Heart Failure 2013

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Presenter Disclosure Information

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I will discuss off label use and/or investigational use in my presentation:

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• Who should treat heart failure patients?
• How should HF be diagnosed?
• What are the current guidelines for heart failure therapy and the evidence supporting them?
• What are the potential new CHF therapies?
Heart Failure 2013

- Who should treat heart failure patients?
- How should HF be diagnosed?
- What are the current guidelines for heart failure therapy and the evidence supporting them?
- What are the potential new CHF therapies?

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Specialty Care in New Onset HF
Predictors of 2-year death or CV admission


<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low EF</td>
<td>1.92</td>
<td>1.27-2.89</td>
<td>.002</td>
</tr>
<tr>
<td>Cardiology care</td>
<td>0.62</td>
<td>0.42-0.93</td>
<td>.02</td>
</tr>
</tbody>
</table>

Non-significant variables in stepwise logistic regression model: age, sex, CAD, A Fib, DM, COPD, PAD
Who Manages HF?

- IM 43%
- FP/GP 29%
- CARD 17%
- Other 11%

Heart Failure 2013

- Who should treat heart failure patients?
- How should HF be diagnosed?
  - Definition of Heart Failure
  - Symptoms and Physical Exam Findings
  - Biomarkers
  - Genetic Cardiomyopathies

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Definition of Heart Failure

- HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

- Because not all patients have volume overload at the time of initial or subsequent evaluation, the term “heart failure” is preferred over the older term “congestive heart failure.”

Diagnosis of Heart Failure

- Symptoms
  - Dyspnea (Exertional, PND, Orthopnea)
  - Cough
  - Fatigue
  - Abd discomfort (bloating, anorexia)
  - Sleep disturbances

- Physical Exam
  - Edema (Legs, Abd, Sacral)
  - Rales, Effusion
  - JVP, HJR/AJR
  - Weight
  - Cool extremities
  - MR murmur
  - S3 (S4)
  - Blood/ pulse pressure
  - Pulsus alternans
“First, strike for the jugular and let the rest go”

- Oliver Wendell Holmes, Jr.

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The Role of BNP in the Diagnosis of HF

- What is BNP?
- Potential roles of diagnostic BNP
  - Screening
  - Diagnosis
  - Management
  - Prognosis
- Types of diagnostic tests
  - BNP
  - NT-proBNP
BNP on Admission May Improve Morbidity in Patients Admitted with Dyspnea


NP-Guided Therapy in CHF: Effect on All-Cause Mortality

NP-Guided Therapy in CHF: Effect on Heart Failure-related Hospitalizations


Effect of BNP-guided therapy on Hospitalizations: Meta-Analysis

Potential Limitations to BNP in the Evaluation of AHF

Teerlink JR. Acute Heart Failure, Braunwald’s Heart Disease. 2008

<table>
<thead>
<tr>
<th>TABLE 24–6</th>
<th>Conditions that Influence B-Type Natriuretic Peptide (BNP) Concentrations</th>
</tr>
</thead>
</table>
| Increased BNP concentrations may be found in: | Age (older)  
Sex (female)  
Ethnicity (black)  
Renal dysfunction  
Myocardial infarction/acute coronary syndromes  
Right-sided heart failure (cor pulmonale, acute pulmonary embolus)  
High output failure (cirrhosis, septic shock) |
| Decreased BNP concentrations may be found in: | Obesity  
Early acute heart failure (less than 1 hr)  
Acute mitral regurgitation  
Mitrail stenosis (in the absence of right ventricular failure)  
Stable NYHA class I patients with decreased LV ejection fraction |


Guideline

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

RAY E. HERSHBERGER, MD,1 JOANNE LINDENFELD, MD,2 LUISA MESTRONI, MD,3,4 CHRISTINE E. SEIDMAN, MD,4 MATTHEW R.G. TAYLOR, MD, PhD,5,6 AND JEFFREY A. TOWBIN, MD

Miami, Florida; Denver, Colorado; Boston, Massachusetts; Houston, Texas


- Family history x3 generations
- Screening for CM in first degree relatives
- Referral to Genetic centers
- Genetic testing of most clearly affected person
- Genetic/Family counseling
- Therapy as per guidelines for type of cardiomyopathy

<table>
<thead>
<tr>
<th>Cardiomyopathy Phenotype</th>
<th>Gene Tests Availablea</th>
<th>Yield of Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM MYH7, MYBPC3, TNN1, TNNT2, MYH6, MYL2, MYL7</td>
<td>MYH7, MYBPC3 each account for 39–49% of mutations, TNNT2 for 19–29%. Genetic case can be identified in 35–45% overall, up to 60–90% when the family history is positive.</td>
<td></td>
</tr>
<tr>
<td>DCM LMNA, MYH7, TNNT2, SCNN1A, DES, MYBPC3, TNN1, TPM1, ACTC, PLN, LDB3 and TM2Z</td>
<td>5.9%, 12%, 29%, for LMNA, MYH7, and TNNT2 respectively. All data are from research cohorts.</td>
<td></td>
</tr>
<tr>
<td>ARVD DSP, PKP2, DSG2, DSG3</td>
<td>6%–10%, 1%–49%, for DSP, PKP2, and DSG2, respectively.</td>
<td></td>
</tr>
<tr>
<td>LVNC Uncertain—see discussion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCM Uncertain—see discussion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Practical Diagnostics in the Evaluation of Heart Failure

• History
  – Etiology: CAD, HTN, Familial, Toxins (EtOH, drugs, chemo, alternative rx, etc.)
  – Symptoms, exercise tolerance (specific personal markers)
• Physical exam: Diagnosis and Monitoring
• Labs include Chem-7, HgbA1c, Ca, Mg, CBC, ferritin/TIBC, TSH, U/A, Lipid profile, LFT
• CXR, ECG
• Echocardiogram: probably single most useful; RVG/MUGA useful at some centers
• Cardiac catheterization: right and left heart
• Other: HIV, sleep disordered breathing, disease specific tests, BNP/ NT-pro-BNP (diagnosis/ risk stratification)

Heart Failure 2013

• Who should treat heart failure patients?
• How should HF be diagnosed?
• What are the current guidelines for heart failure therapy and the evidence supporting them?
• What are the potential next advances in HF treatment?
Current Heart Failure Guidelines

• ACC/AHA 2009
  2013 guidelines IN PRESS!!!

• ESC 2012
  (McMurray JJV, et al. Eur Heart J 2012;33:1787-1847)

• HFSA 2010 (updated on-line)

Clinical Classifications of Heart Failure Severity


<table>
<thead>
<tr>
<th>NYHA Functional Classification</th>
<th>ACC-AHA Stages of Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea</td>
<td>Stage A At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms</td>
</tr>
<tr>
<td>Class II Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea</td>
<td>Stage B Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms</td>
</tr>
<tr>
<td>Class III Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
<td>Stage C Symptomatic heart failure associated with underlying structural heart disease</td>
</tr>
<tr>
<td>Class IV Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased</td>
<td>Stage D Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy</td>
</tr>
</tbody>
</table>

* The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al.† The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association. 1, 2
Stage A HF: “When you’re a hammer, Everything looks like a nail!”

AND THEN I HEARD A LOUD BANG AND WHEN I TURNED BACK HE WAS GONE!
### At Risk for Heart Failure

#### Stage A
- At high risk for HF but without structural heart disease or symptoms of HF
- e.g.: Patients with: hypertension, atherosclerotic disease, diabetes, metabolic syndrome, or patients using cardioxins with HFx CM

#### 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)

#### Therapy
- All measures under stage A

### Stage B
- Structural heart disease but without symptoms of HF
- e.g.: Patients with: NYHA class IIa, reduced LVEF and EF, asymptomatic valvular disease

#### Therapy Goals
- All measures under stages A and B
- Dietary salt restriction
- Drugs for fluid retention
- ACEI
- Beta-blockers

### Stage C
- Structural heart disease with prior or current symptoms of HF
- e.g.: Patients with: known structural heart disease and shortness of breath and fatigue, reduced exercise tolerance

#### Therapy Goals
- All measures under stages A-C
- Diuretics
- Losartan
- B-blockers
- ICDs

### 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
- Appropriate measures under stages A-C
- Decision re: appropriate level of care

### Therapy
- All measures under stages A-C

### Options
- Complimentary and alternative care
- Extraordinary measures

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**Calm down. I'm not a jumper - I'm a smoker.**

![Smoking cartoon](https://www.vskeelse.com)
Risk Factor Modification in HF

- Weight loss
- Smoking cessation
- Hypertension therapies
- Diabetes management
- Lipid control
- Sleep apnea
- Exercise

Lifetime Risk of Heart Failure According to Number of Healthy Lifestyle Factors

- Physicians Health Study cohort (20,900 men)
- Six modifiable risk factors:
  - Maintained Body weight
  - No Smoking
  - Exercise
  - Less Alcohol intake
  - Eats breakfast cereals
  - Eats fruits and vegetables

Importance of Afterload Reduction

Effect of ACE Inhibitors on All-Cause Mortality in Stage A Patients

Effect of ACE Inhibitors on Mortality in Patients With Post MI LV Dysfunction


<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI (Mortality)</th>
<th>Controls (Mortality)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
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<td>AIRE</td>
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<td>6.5%</td>
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</tbody>
</table>
Essential Topics in Patient Education


<table>
<thead>
<tr>
<th>Educational topics</th>
<th>Skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition and aetiology of heart failure</td>
<td>Understand the cause of heart failure and why symptoms occur</td>
</tr>
<tr>
<td>and symptoms of heart failure</td>
<td>Monitor and recognize signs and symptoms</td>
</tr>
<tr>
<td>Symptoms and signs of heart failure</td>
<td>Record daily weight and recognize rapid weight gain</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>Know how and when to notify healthcare provider</td>
</tr>
<tr>
<td>Risk factor modification</td>
<td>Use flexible diuretic therapy if appropriate and recommended</td>
</tr>
<tr>
<td>Diet recommendation</td>
<td>Recognize the common side-effects of each drug prescribed</td>
</tr>
<tr>
<td>Exercise recommendations</td>
<td>Understand the importance of smoking cessation</td>
</tr>
<tr>
<td>Be measured and comfortable about physical activity</td>
<td></td>
</tr>
<tr>
<td>Understand the benefits of exercise</td>
<td></td>
</tr>
<tr>
<td>Perform exercise training regularly</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational topics</th>
<th>Skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity</td>
<td>Be measured about engaging in sex</td>
</tr>
<tr>
<td>and discuss problems with healthcare professionals</td>
<td></td>
</tr>
<tr>
<td>Understand specific sexual problems and various coping strategies</td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td>Receive immunization against infections such as influenza and pneumococcal disease</td>
</tr>
<tr>
<td>Sleep and breathing disorders</td>
<td>Recognize preventive behaviour such as reducing weight of obese, avoiding cessation, and abstinence from alcohol</td>
</tr>
<tr>
<td>Adherence</td>
<td>Learn about treatment options if appropriate</td>
</tr>
<tr>
<td>Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan</td>
<td></td>
</tr>
<tr>
<td>Psychosocial aspects</td>
<td>Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support</td>
</tr>
<tr>
<td>Learn about treatment options if appropriate</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Understand important prognostic factors and make realistic decisions</td>
</tr>
<tr>
<td>Seek psychosocial support if appropriate</td>
<td></td>
</tr>
</tbody>
</table>
**HF-ACTION: Time to Cardiovascular Mortality or Heart Failure Hospitalization**


**Enrollment Criteria:**
- LVEF ≤ 35%
- NYHA II-IV
- Optimal Rx x 6 wks

**Study Groups:**
- Usual Care
- Exercise:
  - 36 supervised sessions in 3 mo
  - Home-based with provided treadmill/ bike and HRM
Precipitants of HF: Medications

- Inappropriate medications
  - Non-Steroidal Anti-Inflammatory Drugs
  - Anti-arrhythmics (non-Amiodarone)

NSAIDs in Heart Failure


107,092 patients surviving first HF hospitalization in Denmark
Similar effect on HF Hospitalizations
Heart Failure Case (1)

- 50 yo man with non-ischemic CM, EF 12%, diabetes mellitus, chronic kidney disease (baseline Cr~1.8)
- 3-4 week h/o progressive wt gain (+25 lbs), resistant to increased oral diuretics
- Presents to OSH ER with massive edema, dyspnea, decreased urination, BP 132/76, HR 88, Cr 3.8, BNP 4200 (no comment on JVP)
ARS #1

Therapeutic interventions should include (choose single “best” answer):
1) Hold furosemide
2) Continue oral dose of furosemide
3) Initiate intravenous furosemide
4) Hold carvedilol

Heart Failure Case (2)

• Pt admitted to OSH:
  – Diuretics, lisinopril, carvedilol discontinued
  – Bedrest for 3 days (gained 1 kg; Cr 4.2)
  – Echo
  – Transferred to SFVAMC for refractory HF/ RF

• At SFVAMC:
  – Exam: JVP to ear, massive edema
  – Furosemide 160 mg iv bolus, 10 mg/hr infusion
  – Lost 11 kg; Cr 4.2 ➞ 2.1
  – Carvedilol reinitiated hosp day 2
Therapeutic Algorithm for Symptomatic Systolic Heart Failure (1)


Pathophysiology of cardiorenal syndrome

Use of Diuretics in Heart Failure Patients

- Self-titration: need “dry” weight on patient’s scale
  - Daily weights (routine; daily log with symptoms, etc.)
  - If weight increased by >3-5 lbs, take double diuretic
  - If patient requires supplemental potassium, also double
  - If worsening at any time or no improvement after 2-3 days, call

- Often increasing creatinine can be evidence of worsening heart failure, elevated CVP and need for more diuretics

- Diuretic resistance may be treated with switch to bumetanide/ torsemide, or adding spironolactone or metolazone

- Many patients may not require diuretics when ACE inhibitor, beta blocker, aldosterone antagonist, etc. are optimized
## Effect of ACE Inhibitors on Mortality Reduction in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td>Post MI</td>
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<tr>
<td><strong>Average</strong></td>
<td>21%</td>
<td>25%</td>
<td><strong>0.78 (0.67–0.91)</strong></td>
</tr>
</tbody>
</table>


## Use of ACE Inhibitors in Heart Failure Patients

- Indicated in potentially ALL pts with HF and EF≤40%
- Some ACE Inhibitor is better than none
- Start low dose, up-titrate q2 wks or so; check labs within 1-2 weeks of dose adjustment, then about q4 months
- Asymptomatic low blood pressure: usually no change
- Symptomatic Hypotension: often improves with time (reassure); re-evaluate other meds (nitrates, diuretics, etc.)
- Cough: Other causes, rechallenge, consider ARB
- Worsening renal function: Smaller of an increase in creatinine up to 50% above baseline or 3 mg/dL or eGFR <25 ml/min/1.73m² is acceptable; K<5.5
- ARBs are probably INFERIOR to ACEi in CHF
The Challenge for CHF Therapeutics

World Death Rate Holding Steady At 100 Percent

The Onion

Beta-Blockers in HF
Effect on Mortality

Modified from: Teerlink JR, Massie BM. Am J Cardiol 1999; 84:94R-102R.
Use of Beta blockers in Heart Failure Patients

- Indicated in potentially ALL pts with HF and EF ≤ 40%
- Some beta blocker is better than none; Some beta blocker probably better than more ACE inhibitor
- Start low dose, up-titrate q2 wks or so; check labs within 1-2 weeks of dose adjustment, then about q4 months
- Severe asthma is a contraindication (NOT COPD)
- Asymptomatic low blood pressure: usually no change
- Symptomatic Hypotension: often improves with time (reassure); re-evaluate other meds (nitrates, diuretics, etc.)
- Worsening HF: Congestion, Increase diuretic; Fatigue, usually reassurance
- Low heart rate: if <50 bpm, halve dose
- Other beta blocker side effects minimal in HF patients

Eplerenone Improves Survival in Patients with HF (EMPHASIS-HF)


2737 patients
NYHA II
LVEF ≤ 35%
Randomized to Eplerenone (≤ 50 mg qd) or Placebo
K+ > 5.5 in 11.8% Epl vs 7.2% Placebo (p < 0.001)
Use of Mineralocorticoid Receptor Antagonists (MRAs) in HF Patients

- Indicated in potentially ALL NYHA II-IV pts with HF and EF≤35%
- Start low dose, up-titrate after q4-8 wks or so; check labs within 1 and 4, 8 and 12 weeks of dose adjustment, at 6,9,12 months, and then q4 months
- Avoid potassium repletion and K-containing salt substitutes
- Hyperkalemia: If K>5.5 or Cr≥2.5 mg/dL, halve dose and f/u; if K>6.0 or Cr >3.5 mg/dL, d/c dose and f/u. Consider rechallenge if reversible cause identified.
- Gynecomastia in males: change to eplerenone

Evidence-Based Pharmacologic Treatment of Heart Failure


<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaptoprilP</td>
<td>6.25 t.i.d.</td>
<td>50 t.i.d.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 b.i.d.</td>
<td>10–20 b.i.d.</td>
</tr>
<tr>
<td>LisinoprilP</td>
<td>2.5–5.0 o.d.</td>
<td>20–35 o.d.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 o.d.</td>
<td>5 b.i.d.</td>
</tr>
<tr>
<td>TrandolaprilP</td>
<td>0.5 o.d.</td>
<td>4 o.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 a.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 b.i.d.</td>
</tr>
<tr>
<td>Metoprolol succinate (CR/XL)</td>
<td>12.5/25 o.d.</td>
</tr>
<tr>
<td>NebivololP</td>
<td>1.25 a.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4 or 8 a.d.</td>
</tr>
<tr>
<td>valsartan</td>
<td>40 b.i.d.</td>
</tr>
<tr>
<td>LosartanH</td>
<td>50 o.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone</td>
<td>25 o.d.</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 o.d.</td>
</tr>
</tbody>
</table>
Therapeutic Algorithm for Symptomatic Systolic Heart Failure (2)


Still NYHA class II–IV and LVEF ≤35%?

- Yes
- No

QRS duration ≥ 120 ms?

- Yes
- No

Consider CRT-P/CRT-D

Consider ICD

Still NYHA class II–IV?

- Yes
- No

No further specific treatment; Continue in disease-management programme

Consider digoxin and/or H-SDN
If end stage, consider LVAD and/or transplantation

Device Therapy
SCD-HeFT: All-Cause Mortality

**Enrollment Criteria**
2,521 patients
Moderately symptomatic HF (NYHA II or III)
LVEF ≤35%

**Study Groups:**
Placebo
Amiodarone (200/300/400 qd)
ICD (VF only)

**2009 ACC/ AHA Guidelines: Patients With Reduced LV Ejection Fraction**

**Primary Prevention: Implantable Cardioverter-Defibrillator**

ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-myocardial infarction, have an LVEF less than or equal to 35%, with NYHA functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year.
CARE-HF: Primary Endpoint

Enrollment Criteria
813 Patients
Symptomatic HF (NYHA III/ IV)
LVEF ≤35%
LVEDD>30 mm
QRS>120 msec

Study Groups:
Medical therapy
CRT

CARE-HF: All-Cause Mortality

No. at Risk
Cardiac resynchronization
409 376 351 213 89 8
Medical therapy
404 365 321 192 71 5

P<0.002

Days

CARE-HF: Primary Endpoint

Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than or equal to 0.12 seconds, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated.

MADIT-CRT: Kaplan-Meier Estimates of the Probability of Survival Free of Heart Failure

Enrollment Criteria:
Age >21 years
LVEF≤30%
NYHA class I or II
Ischemic/ Non-isch  
(only NYHA II)
QRS duration ≥130 msec

Study Groups:
(2:3 randomization)
ICD only
ICD + CRT

MADIT-CRT: Risk of Death or Heart Failure, According to Selected Sub-Groups


Cardiac Resynchronization Therapy in NYHA Class II Patients

Therapeutic Algorithm for Symptomatic Systolic Heart Failure (2)


Still NYHA class II-IV and LVEF ≤35%?

Yes

No

QRS duration ≥120 ms?

Yes

Consider CRT-P/CRT-D

No

Consider ICDf

Still NYHA class II-IV?

Yes

No

No further specific treatment.
Continue in disease-management programme

Consider ‘digoxin’ and/or ‘β-blockers’
If end stage, consider LVAD and/or transplantation

CHARM-Added: Primary outcome
CV death or CHF hospitalisation


Placebo

Candesartan

HR 0.85 (95% CI 0.75-0.96), p=0.011

Adjusted HR 0.85, p=0.010

Number at risk

Candesartan 1276 1176 1063 948 457

Placebo 1272 1136 1013 906 422

0 10 20 30 40 50

%
Effects of Digoxin on Survival


Figure 3. All-Cause Mortality Rates by Serum Digoxin Concentration Groups

<table>
<thead>
<tr>
<th>Serum Digoxin Concentration, ng/mL</th>
<th>Mortality Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 ≥2.0</td>
<td>[Graph showing mortality rates across different concentration levels]</td>
</tr>
</tbody>
</table>

Hazard ratio 0.57 (43% reduction)

A-HeFT: All-Cause Mortality


I+H: 32 Deaths (6.2%)
P: 54 Deaths (10.2%)
Hazard ratio 0.57 (43% reduction)

No. at Risk
Placebo | 532 | 466 | 401 | 340 | 285 | 232 | 24
Isosorbide dinitrate plus hydralazine | 518 | 463 | 407 | 359 | 313 | 251 | 13
Management of Co-morbidities in Patients with Stage C HF

- Hypertension
- Hyperlipidemia
- Obesity
- Coronary artery disease
- Peripheral vascular disease
- Diabetes mellitus
- Chronic obstructive pulmonary disease
- Sleep apnea
- Depression
- Atrial fibrillation

Maintenance of Sinus Rhythm in Heart Failure: AF-CHF

Enrollment Criteria:
Age >18 years
LVEF ≤35%
Hosp with HF
h/o HF NYHA II - IV
h/o atrial fib episode >6h
or with cardioversion

Study Groups: Unblinded
Rhythm-control
Rate-control

HR = 1.06; 95% confidence interval, 0.86 to 1.30; P=0.59 by log-rank test

**Maintenance of Sinus Rhythm in Heart Failure: AF-CHF**


![Graph A: Cardiovascular Death](image1)

- **A**: Cardiovascular Death
  - Hazard ratio 0.998 (0.894-1.238)
  - p = 0.983

![Graph B: Total Mortality](image2)

- **B**: Total Mortality
  - Hazard ratio 1.051 (0.887-1.274)
  - p = 0.615

**ANDROMEDA: Dronedarone in Chronic Heart Failure**


**Enrollment Criteria:**
- Age >18 years
- Hosp with HF
- Episode of dyspnea (NYHA III or IV)
- Wall motion index ≤1.2 (approx LVEF ≤35%)

**Study Groups:**
- Placebo
- Dronedarone (400 mg po bid)

**Trial stopped early for safety concerns**
- Only 617 patients of planned 1000 enrolled with median follow-up of only 2 months

**Results:**
- **HR = 2.13; 95% confidence interval (CI), 1.07 to 4.25; P = 0.03**

![Graph B: All-Cause Mortality](image3)

- **B**: All-Cause Mortality
Remote Patient Monitoring in Heart Failure Management: Parameters Monitored


Remote Patient Monitoring in Heart Failure Management: Effect on All-cause Mortality

Remote Patient Monitoring in Heart Failure Management: Effect on HF Hospitalizations


Remote Patient Monitoring in Heart Failure Management: Effect on All Hospitalizations

## Multidisciplinary Approaches to HF Management


<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>HF Hospital</th>
<th>All Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multidisc F/U</strong></td>
<td>0.75* (0.59-0.96)</td>
<td>0.74* (0.63-0.87)</td>
<td>0.81* (0.71-0.92)</td>
</tr>
<tr>
<td><strong>Multidisc Self-care</strong></td>
<td>1.14 (0.67-1.97)</td>
<td>0.66* (0.52-0.83)</td>
<td>0.73* (0.57-0.93)</td>
</tr>
<tr>
<td><strong>Telephone &amp; 1° Care</strong></td>
<td>0.91 (0.67-1.29)</td>
<td>0.75* (0.57-0.99)</td>
<td>0.98 (0.80-1.20)</td>
</tr>
</tbody>
</table>

Relative Risk (95% Confidence intervals)

## An Approach to Management of Patient with Stage C Symptomatic HF-REF

- Control volume overload with diuretics
- Initiate ACE inhibitor therapy (2.5-5 mg lisinopril); substitute with ARB only if absolutely necessary
- Initiate Beta blocker therapy (prefer Carvedilol 3.125 or 6.25 mg po bid) and up-titratio to max
- Initiate spironolactone (switch to eplerenone if needed)
- Maximize ACE inhibitor
- If after stable therapy and meets criteria, ICD/CRT
- If still symptomatic, initiate digoxin (earlier if AF)
- If still symptomatic, consider ARB or ISDN/ Hydral
Heart Failure with Reduced EF

Only part of the problem...

Prevalence of Heart Failure with Preserved EF

<table>
<thead>
<tr>
<th>Study</th>
<th>EF &gt; 50%</th>
<th>EF &gt; 50%</th>
<th>EF &gt; 45%</th>
<th>EF &gt; 50%</th>
<th>EF &gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham (N=73)</td>
<td>51</td>
<td>43</td>
<td>78</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>Olmstead (N=137)</td>
<td>43</td>
<td>20</td>
<td>57</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>CHS Prevalence (N=269)</td>
<td></td>
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<tr>
<td>CHS Incidence (N=597)</td>
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<tr>
<td>NHF Project (N=6,700)</td>
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</tbody>
</table>

Percent of Patients
Prognostic Importance of Diastolic Dysfunction


Moderate/Severe diastolic dysfunction: HR 10.2 (3.3-31)

Mechanisms for Diastolic Dysfunction


Delayed relaxation (τ)

Increased stiffness (chamber compliance)
**Diagnosis of Diastolic Heart Failure/ HFPEF**

- Confirm EF (assure test quality)
- Exclude non-cardiac causes (Hx, PE, chest Xray, labs to exclude pulmonary disease, anemia, deconditioning, various causes of edema)
- Echo to exclude valvular, pericardial, cardiomyopathic causes (HCM, restrictive CM), and to evaluate for substrate for DHF (LVH, LA enlargement)
- Stress test or angiography for selected patients
- Specific measurements of diastolic function not necessary and may be misleading

---

Stage C: Preserved EF with Symptoms


Recommended Therapies for Routine Use:

- Treating known risk factor (hypertension) with therapy consistent with contemporary guidelines
- Ventricular rate control for all patients
- Drugs for all patients -
  - Diuretics
- Drugs for appropriate patients –
  - ACEI
  - ARBs
  - Beta-Blockers
  - Digitalis
- Coronary revascularization in selected patients
- Restoration/maintenance of sinus rhythm in appropriate patients

Randomized Controlled Trials of Therapies for HF with Preserved EF

- CHARM-Preserved
- PEP-CHF
  (Cleland JG, et al. Er Heart J 2006;27:2338-45.)
- I-PRESERVE
I-PRESERVE: Kaplan-Meier Curves for the Primary Outcome


Primary Outcome:
Death from any cause
Hospitalization for:
• Worsening HF
• Myocardial infarction
• Stroke
• Atrial arrhythmia
• Ventricular arrhythmia

In-hospital:
• Myocardial infarction
• Stroke

HR = 0.95 [0.86 to 1.05; p=0.35 by log-rank]

RAS Inhibition in Heart Failure with Preserved Ejection Fraction (HF-PEF)


Pooled effect on All-cause Mortality

Pooled effect on HF Hospitalization
STICH Hypothesis 1: CABG vs Medical Therapy


- 1,212 pts EF≤35%, CAD ammenable to CABG
- Randomized to CABG vs Medical Rx
- Median f/u: 56 mo
- 17% of pts in MedRx group had CABG
Rare Complications of Heart Transplantation

"Just so you know for next time, when we do a biopsy we only take a tiny piece."
Stage D Therapies: Refractory End-Stage Heart Failure


Recommended Therapies Include:
- Control of fluid retention
- Referral to a HF program for appropriate pts
- Discussion of options for end-of-life care
- Informing re: option to inactivate defibrillator
- Device use in appropriate patients
- Surgical therapy –
  - Cardiac transplantation
  - Mitral valve repair or replacement
  - Other
- Drug Therapy –
  - Positive inotrope infusion as palliation in appropriate patients

Continuous-flow Ventricular-Assist Device

Continuous-flow Ventricular-Assist Device


Enrollment Criteria:
- Transplant listed
- Body Surface Area (BSA) > 1.2 m²
- NYHA class IV HF sx
- On inotropic support, if tolerated
- Listing as Status 1A/1B

CHF Therapies

UCSF
**Management of Systolic Heart Failure**

- Stage A: High Risk
- Stage B: LV Dysfxn
- Stage C: Symptomatic HF
- Stage D: End-Stage HF

**Rx risk factors, limit Na, limit alcohol, monitor weight, activity Rx**

- Diuretics
- Beta-Blockers
- ACE Inhibitors (ARB if intolerant or as additional therapy)
- Nitrates/ hydralazine
- Aldosterone Antagonists
- Digoxin (Low dose; Rate control or Sx)
- HTN

**Transplantation**

**IV inotropes; LVAD**

Heart Failure 2013

- Who should treat heart failure patients?
- How should HF be diagnosed?
- What are the current guidelines for heart failure therapy and the evidence supporting them?
- What are the potential new CHF therapies?
New Treatments for HF

- Inhibitors of the RAAS system
  - Vasopeptidase inhibitors
  - Renin inhibitors
- If channel blockers (ivabradine)
- Endothelin receptor antagonists
- Cytokine antagonists/ Immune modulation
- Vasopressin antagonists, Diuretics and Aquaretics
- Sarcomere-based positive inotropic agents
- Myocardial metabolic modulators
- Hormone therapies
- Stem cell-based therapies

Thank you!
Heart Failure Society of America

www.hfsa.org