Complex Heart Failure – Inpatient and Outpatient Management

Foundations for Practice Excellence: Core Curriculum for the Cardiovascular Clinician

Washington, DC
September 17, 2016

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Disclosures: none
ARS Question #1

By 2013, what % of the U.S. population will be over 65 years old?

A. 5%
B. 10%
C. 15%
D. 20%
E. 25%
Number of Patients With Heart Failure Will Continue to Increase

Number of persons over the age of 65 expected to double in 30 years

Percentage of people over the age of 65 is steadily increasing

- 1940 6.8%
- 1970 9.8%
- 2000 12.4%
- 2030 (predicted) 19.7%

*The lifetime risk of developing HF is 20% for Americans ≥40 years of age

Incidence of Heart Failure by Age

*The Framingham Heart Study*

Adapted from Ho et al. *J Am Coll Cardiol* 1993

**Annual CHF Incidence**

- **Men**
- **Women**

Age (Years):
- 30-39
- 40-49
- 50-59
- 60-69
- 70-99

Adapted from Ho et al. *J Am Coll Cardiol* 1993
Prevalence of heart failure by sex and age

Go A S et al. Circulation 2013;127:e6-e245
Hospital discharges for heart failure by sex 1980–2010

Trends in Hospitalizations and Outcomes for Acute Cardiovascular Disease and Stroke, 1999–2011

<table>
<thead>
<tr>
<th></th>
<th>Relative change (%)</th>
<th>30 day mortality</th>
<th>1 yr mortality</th>
<th>readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Krumholz H M et al. Circulation. 2014;130:966-975

1: Hospitalization rate per 100,000 person-years (#), 2: 30-day mortality (%), 3: 1-year mortality (%), and 4: 30-day readmission (%).
Adjusted annual changes in rates of hospitalization by conditions and subgroups, 1999 to 2011.

Krumholz H M et al. Circulation. 2014;130:966-975
Reasons for the improvement in outcomes

- Improvements in the identification and treatment of hypertension
- Rise in the use of statins
- Marked declines in smoking
- Improvements in the use of evidence-based medications
- Timeliness of treatment for patients with ST-segment–elevation myocardial infarction
- Quality improvement initiatives directed toward these conditions and the use of registries and other data to track performance and to support improvement efforts
- Publicly reported measures for myocardial infarction and heart failure
Inpatient or Outpatient?
Multimorbidity is common in patients with HF
Number of Chronic Conditions in Medicare FFS Beneficiaries 2010

Figure 1.2a Percentage of Medicare FFS Beneficiaries by Number of Chronic Conditions: 2010

- 0 to 1: 32%
- 2 to 3: 32%
- 4 to 5: 23%
- 6+: 14%
First Geographic Point of Care

- Inpatient Unit on Obs Status: 2%
- Observation Unit: 1%
- Inpatient Unit: 20%
- ED: 77%

Heart Failure Presentations

1: Gradual onset of effort intolerance: dyspnea, CP, fatigue (+/- volume overload: abd distension, edema)

2: Worsening chronic HF with either reduced or preserved LV systolic function

2: Advanced HF with severe LV systolic dysfunction

3: Acute HF: sudden increase in BP, MI/ischemia, arrhythmias
Current Symptoms
Acute dyspnea: shortness of breath at rest or with minimal exertion that generally develops over time, not abruptly
Dyspnea on exertion (dyspnea with mild to moderate exertion)
Cough (generally nonproductive or minimal sputum)
Altered mental status (secondary to decreased perfusion or PaO$_2$)
Recent weight gain
Fatigue
Exertion-related chest pain
Weight Change Preceding HF Hospitalization

Chaudhary et al  Yale University 2006
Diagnosis of ADHF

Medical History

Prior history of CHF; taking medication for CHF
Prior history of MI, angina, coronary artery disease, HTN
Prior history of obstructive valvular heart disease or cardiomyopathy
Nonadherence with prescribed medication, dietary indiscretion, or recent NSAID use
FH is important!

*****SOME PATIENTS MAY HAVE NO PRIOR HISTORY OF HEART FAILURE!
In patients with idiopathic dilated cardiomyopathy, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial dilated cardiomyopathy.

Table 2. Evaluation of the Cause of Heart Failure: The History

<table>
<thead>
<tr>
<th>History to include inquiry regarding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Coronary or peripheral vascular disease</td>
</tr>
<tr>
<td>Myopathy</td>
</tr>
<tr>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>Mediastinal irradiation</td>
</tr>
<tr>
<td>History or symptoms of sleep-disordered breathing</td>
</tr>
<tr>
<td>Exposure to cardiotoxic agents</td>
</tr>
<tr>
<td>Current and past alcohol consumption</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Exposure to sexually transmitted diseases</td>
</tr>
<tr>
<td>Thyroid disorder</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history to include inquiry regarding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition to atherosclerotic disease</td>
</tr>
<tr>
<td>(Hx of MIs, strokes, PAD)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Myopathy</td>
</tr>
<tr>
<td>Conduction system disease (need for pacemaker)</td>
</tr>
<tr>
<td>Tachyarrhythmias</td>
</tr>
<tr>
<td>Cardiomyopathy (unexplained HF)</td>
</tr>
<tr>
<td>Skeletal myopathies</td>
</tr>
</tbody>
</table>

HF indicates heart failure; Hx, history; MI, myocardial infarction; and PAD, peripheral arterial disease.
Diagnosis of ADHF

**Examination**

Rales

Tachycardia

$S_3$ gallop and/or murmur suggesting obstructive or regurgitant valvular disease

Pedal edema

JVD or other evidence of increased LV filling pressure (hepatojugular reflex, ascites, hepatomegaly)

Increased LV filling pressure ($\geq 20$ mg Hg) confirmed by pulmonary artery catheter
Differential Diagnosis
Pulmonary infection
Acute COPD/asthma exacerbation
Reactive airway disease
Acute coronary syndrome
Pulmonary emboli
Pneumothorax, pleural effusions
Aortic dissection
ARS Question #2

Markers of poor prognosis in patients hospitalized with HF include:

A. Change in weight
B. S3 gallop
C. Hypotension
D. AKI
E. A+B
F. C+D
ADHERE® CART: Predictors of Mortality

Highest to Lowest Risk Cohort
OR 12.9 (95% CI 10.4-15.9)

Biomarkers

In ambulatory patients with dyspnea, measurement of BNP or NT-proBNP is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (class I, LOA A).

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (class I, LOA A).

BNP- or NT-proBNP-guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program (class IIa, LOA B).

The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established (class IIb, LOA B).

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (class IIb, LOA B).
Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis (class I, LOE A)

Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF (class I, LOE A)

The usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated HF is not well established (IIb, LOE C)

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF (IIb, LOE A)
Initial Assessment: Other testing

12 lead ECG
Chest x-ray
2D echocardiogram with doppler
Noninvasive imaging to detect ischemia/viability
Coronary arteriography in patients presenting with HF who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind

Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF:
1) who have had a significant change in clinical status;
2) who have experienced or recovered from a clinical event; or who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or
3) who may be candidates for device therapy.
Hemodynamic monitoring

Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment. (class I, LOE C)

Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies and

- a. whose fluid status, perfusion, or systemic or pulmonary vascular resistance is 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 require parenteral vasoactive agents; or
- e. who may need consideration for MCS or transplantation. (IIa, LOE C)
Initial Assessment : Class III

- Routine endomyocardial biopsy. Endomyocardial biopsy should be performed only if the results would influence therapy.

- Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions.

- Routine hemodynamic monitoring.
Rapid Assessment of Hemodynamic Status

Congestion at Rest

Low Perfusion at Rest

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Warm &amp; Dry</td>
<td>Warm &amp; Wet</td>
</tr>
<tr>
<td>(Low Profile)</td>
<td>(Complex)</td>
</tr>
<tr>
<td>L</td>
<td>C</td>
</tr>
<tr>
<td>Cold &amp; Dry</td>
<td>Cold &amp; Wet</td>
</tr>
</tbody>
</table>

Congestion
- Orthopnea / PND
- JVD
- Hepatomegaly
- Edema
- Rales
- Elevated est. PA systolic
- Valsalva square wave

Low Perfusion
- Narrow pulse pressure
- Sleepy / obtunded
- Low serum sodium cause

Cool extremities
- Hypotension
- Renal Dysfunction (one cause)
Acute CHF Management: A Proposed Guideline

Identify the cause
- ischemia/infarct, HTN, intercurrent illness, diet/medication noncompliance, etc.

Assess volume status

Acute therapy: oxygen, diuretics, consider vasoactive therapy
"The importance of blood-letting, as a medicinal agent, in comparison with other means of cure, is shown in various respects...it is the least equivocal of remedies: its good effects, when properly administered, are, in most cases, so immediate and striking as not to be mistaken...In short, blood-letting is a remedy which, when judiciously employed, it is hardly possible to estimate too highly."

On the Proper Administration of Blood-Letting, for the Prevention and Cure of Disease, (London, 1840) by Henry Clutterbuck, M.D., Member of the Royal College of Physicians.*

Anatomical points for Bloodletting: Castellani, Giovani Marie (1585-1655). Filactirion della flebotomia et arteriotomia... (Viterbo, 1619).*

Instruments used in Blood Letting: Scultetus, Johannes (1595-1645). Armamentarium hirurgicum... (Lugdunum Batavorum, 1693).*

Leach Bowl: Bossche, Willem van den. Historia Medica (Bruxellae,1639). (Image from: Lyons & Petrucelli. Medicine, an illustrated history. (New York, 1975).)

* From the UCLA Biomedical Library: www.library.ucla.edu/libraries/biomed
Morphine
Oxygen
Lasix
Tourniquets

“MOLT”
**Rotating Tourniquets**

*Fig. 10-10. Rotating tourniquet technique. Timing of compression and release of extremities and the sequence of rotation and sequence of removal of tourniquet during a course of tourniquet therapy which was prescribed for 1 hour starting at 2 A.M. Anatomy shown in figures indicates extent of circulation.*
Most Common IV Medications
All Enrolled Discharges (n=105,388) October 2001-January 2004

- IV Diuretic: 88%
- Dobutamine: 6%
- Dopamine: 6%
- Milrinone: 3%
- Nesiritide: 10%
- Nitroglycerin: 10%
- Nitroprusside: 1%
Evidence of Incomplete Relief From Congestion

20% of ADHF patients discharged with weight gain or no change in weight

Note: For the chart, n represents the number of patients who have both baseline and discharge weight, and the percentage is calculated based on the total patients in the corresponding population. Patients without baseline or discharge weight are omitted from the histogram calculations.
Profiles and Therapies of Advanced Heart Failure

**Congestion at Rest**

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and Dry</td>
<td>PCW normal</td>
<td>CI normal</td>
</tr>
<tr>
<td>Cold and Dry</td>
<td>PCW low/normal</td>
<td>CI decreased</td>
</tr>
<tr>
<td>Warm and Wet</td>
<td>PCW elevated</td>
<td>CI normal</td>
</tr>
<tr>
<td>Cold and Wet</td>
<td>PCW elevated</td>
<td>CI decreased</td>
</tr>
</tbody>
</table>

**Vasodilators**
- Nitroprusside
- Nitroglycerine
- Nesiritide

**Inotropic Drugs**
- Dobutamine
- Milrinone
- Calcium Sensitizers

R. Bourge, UAB Cardiology (adapted from L. Stevenson)
Stevenson LW. *Eur J Heart Failure* 1999;1:251-257
### Current Intravenous Therapies for Heart Failure

<table>
<thead>
<tr>
<th>Effect</th>
<th>Nesiritide</th>
<th>Nitroglycerin</th>
<th>Nitroprusside</th>
<th>Dobutamine</th>
<th>Milrinone</th>
<th>IV Diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilator</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inotropy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chronotropy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Diuretic</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Beneficial effect on RAAS</td>
<td>++</td>
<td>?</td>
<td>↑ renin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Proarrhythmia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tachyphylaxis</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Toxic metabolites</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Titration required</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = positive effect; ++ = strongly positive effect; - = no effect; ? = unknown effect.

Acute CHF Management: A Proposed Guideline

Identify the cause
- ischemia/infarct, HTN, intercurrent illness, diet/medication noncompliance, etc.

Assess volume status

Acute therapy: oxygen, diuretics, consider vasoactive therapy

Close monitoring of progress; daily weights!!!
A Cornerstone of CHF Management
Hoyer Lift Scales: Get the Weight However You Can!
Sigh daily at the same time after voiding and record.
Notify physician if weight gain is 2-3 pounds overnight or 5 pounds in one week

<table>
<thead>
<tr>
<th>Admission Weight</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
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<tbody>
<tr>
<td>Weight</td>
<td>416.5</td>
<td>416.5</td>
<td>404.6</td>
<td>396.1</td>
<td>379.1</td>
<td>367.2</td>
<td>358.8</td>
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<tr>
<td>Date &amp; Time</td>
<td>4/8/12</td>
<td>4/9/12</td>
<td>4/10/12</td>
<td>4/11/12</td>
<td>4/12/12</td>
<td>4/13/12</td>
<td>4/14/12</td>
</tr>
<tr>
<td>Weight</td>
<td>358.8</td>
<td>356.8</td>
<td>344.3</td>
<td>331.5</td>
<td>292.9</td>
<td>290.2</td>
<td>290.2</td>
</tr>
<tr>
<td>Date &amp; Time</td>
<td>4/15/12</td>
<td>4/16/12</td>
<td>4/17/12</td>
<td>4/18/12</td>
<td>4/19/12</td>
<td>4/20/12</td>
<td>4/21/12</td>
</tr>
</tbody>
</table>

This is not a permanent chart form

C:\Documents and Settings\SWEHEE\Desktop\Kate\06\print\Frequently Used Use Form\weight chart for patients.doc

St. Vincent HEART CENTER
Proud of Our Physician Owners
Acute CHF Management: A Proposed Guideline

Identify the cause
- ischemia/infarct, HTN, intercurrent illness, diet/medication noncompliance, etc.

Assess volume status

Acute therapy: oxygen, diuretics, consider vasoactive therapy

Close monitoring of progress; daily weights!!

Optimize chronic therapy
Examples of remodeling

Stage A
- Dilated cardiomyopathy
- Hypertensive or diabetic heart disease

Stage B, C, D
- LV dilatation, Globular shape
- Systolic LV dysfunction
- Mitral regurgitation

Stage B, C, D
- Normal cavity size, Concentric LVH
- Diastolic dysfunction
- Enlarged left atrium
### Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>High risk of developing HF</td>
<td>Asymptomatic HF No symptoms</td>
</tr>
<tr>
<td>B</td>
<td>II–III</td>
</tr>
<tr>
<td>Structural heart disease but without symptoms of HF</td>
<td>Mild and Moderate HF Symptoms upon mild to moderate exertion</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>Structural heart disease with HF symptoms, either <em>prior</em> or <em>current</em> Refractory HF requiring specialized interventions</td>
<td></td>
</tr>
</tbody>
</table>

**IV (D)**: Refractory HF requiring specialized interventions

**III (C)**: Structural heart disease with HF symptoms, either *prior* or *current*

**II (B)**: Structural heart disease but without symptoms of HF

**I (A)**: High risk of developing HF
Stage C: Pharmacologic Therapy

HF/eEF Stage C
NYHA Class I – IV
Treatment:

Class I, LOE A
ACEI or ARB AND
Beta Blocker

For all volume overload, NYHA class II-IV patients

Add

Class I, LOE C
Loop Diuretics

Add

Class I, LOE A
Hydral-Nitrates

Add

For persistently symptomatic African Americans, NYHA class III-IV

Class I, LOE A
Aldosterone Antagonist

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL
### Effect of ACE Inhibitors on Mortality 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><strong>Chronic CHF</strong></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><strong>Post MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td>5%</td>
<td>6.5%</td>
<td>0.75 (0.40–1.11)</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>21%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>
Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF

Trials of ACEI in Heart Failure  ACEI (n = 3870) Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trials  JAMA 1995;273:1450-1456
Impact of ACE Inhibitors on Mortality in Heart Failure Patients with Renal Insufficiency

20,902 patients with Medicare hospitalized with LVEF < .40
ACE Inhibitor use compared to no use
Frances Arch Intern Med 2000;160:2645-2650
Effect of Carvedilol in Severe Heart Failure

COPERNICUS

**Follow-up (months)**

0  2  4  6  8  10  12

**Survival Proportion**

100  95  90  85  80  75  70

Carvedilol  Placebo

HR 0.65 (0.52-0.81)  P=0.0001

n=1133  n=1156

Packer  NEJM 2001;344:1651-8
Safety of Initiating Carvedilol in Patients with Severe Heart Failure

Permanent Withdrawals

% Patients Permanently Withdrawn

Placebo

Carvedilol

$P = 0.02$

Packer  NEJM 2001;344:1651-8
Effect of Carvedilol Dose on Mortality

Carvedilol Dose-Response Trial (MOCHA)

Dose Response of Carvedilol in moderate heart failure patients on all cause mortality
Bristow Circulation 1996;94:2807
Aldosterone Blockade in Heart Failure

RALES: Randomized Aldactone Evaluation Study

Randomized to Aldactone 25 mg PO qd vs Placebo

NEJM 1999;341:709-17
Effect of Digoxin on Mortality in Heart Failure
The DIG Trial

- CV Mortality: 0%
- CHF Hospitalizations: 28%
- Total Hospitalizations: 6%

6788 patients with Class I - III Heart Failure  Digoxin vs Placebo added to ACEI and diuretics
The Digitalis Investigation Group N Engl J Med 1997;336:525-533
Rathore et al. *NEJM* 2002;347:1403

The DIG trial

Increased rate of death for women
Potential Explanations for an Interaction Between Female Sex and Digoxin

Lower creatinine clearance in women

(older with same BMI – less lean body mass)
• Dig levels higher in women @ 30 days (0.9 vs 0.8) but not after 30 days

Lower serum K+

(diuretic use 88% in women vs 80% in men)
• No data on serum K+

Interaction with progestin and p-glycoprotein

(no data on progestin use-probably <10%)
• in BEST mean age 62-23% on E/P but only 6% on a progestin)

Chance
ARS Question #3

Valsartan/sacubitril should be initiated in hospitalized patients.

A. Yes
B. No
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

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

Neprilysin inhibition

Inactive metabolites

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention
LCZ696: Angiotensin Receptor Neprilysin Inhibition
valsartan/sacubitril

“Entresto™”

Angiotensin receptor blocker + Inhibition of neprilysin

St. Vincent HEART CENTER
Proud of Our Physician Owners
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>246</td>
<td>236</td>
</tr>
</tbody>
</table>
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Important considerations:
• the trial randomized only patients who successfully completed a single-blind run-in phase consisting of enalapril for two weeks and then LCZ699 for twice that long—all after being stable for at least a month on either an ACE inhibitor or angiotensin-receptor blocker (ARB)
• the mean blood pressure was 122 mm Hg– pretty substantial when the systolic BP could be as low as 100 mm Hg at enrollment and 95 mm Hg at randomization.
• the vast majority of patients – roughly 70% - had NYHA class II symptoms at enrollment suggests that the patients were pretty stable.
• A minority of patients were enrolled at sites in the United States, which accounts for the low numbers of patients with ICD and CRT devices – 15% and 7% respectively.
• Cost will clearly play a role
### Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF/EF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HF/EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
</tbody>
</table>

### Harm

| III: Harm | B-R | ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32). |
| III: Harm | C-E0 | ARNI should not be administered to patients with a history of angioedema. |
HF ACTION All-Cause Mortality or All-Cause Hospitalization

**Event Rate vs. Years from Randomization**

- **Usual Care**
- **Exercise**

*Adjusted for key prognostic factors*

O'Connor, C. M. et al. JAMA 2009;301:1439-1450
Stage C: Nonpharmacologic Interventions

Class I

• Patients with HF should receive specific education to facilitate HF self-care *(LOE B)*

• Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status *(LOE A)*

Class Ila

• Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms *(LOE C)*

• Continuous positive airway pressure can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea *(LOE B)*

• Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, health-related quality of life, and mortality *(LOE B)*
The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to expand coverage for cardiac rehabilitation services under 42 C.F.R. § 410.49(b)(1)(vii) to beneficiaries with stable, chronic heart failure defined as:

- patients with left ventricular ejection fraction of 35% or less and
- New York Heart Association (NYHA) class II to IV symptoms despite being on optimal heart failure therapy for at least six weeks.
- Stable patients are defined as patients who have not had recent (≤6 weeks) or planned (≤6 months) major cardiovascular hospitalizations or procedures.
About half of the patients (48%) had HFrEF and half (52%) had HFpEF. At the time of hospital discharge, 12.2% of patients with HFrEF and 8.8% of the patients with HFpEF were referred for cardiac rehabilitation.

Compared with other patients, those who were referred were younger (mean age 70 vs 74) with fewer comorbid conditions, and they were more likely to be men (57% vs 51%) and less likely to be covered by Medicare.

Younger age and CABG, PCI (with or without a stent), or cardiac valve surgery were associated with higher odds of being referred for cardiac rehabilitation, consistent with guideline recommendations and insurance coverage.

Stage D

- Fluid restriction, esp for patients with hyponatremia (IIa)
- Inotropic support
  - Short term support for hospitalized patients (IIb)
  - Palliative care (IIb)
  - Use long term outside of palliative care (III)
  - Use for hospitalized patients without low output (III)

- Mechanical circulatory support (IIa)
- Cardiac transplantation (I)
## Acute Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Goals</th>
<th>Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early diagnosis</td>
<td>Vasodilators</td>
</tr>
<tr>
<td>Improvement of hemodynamics and Sx</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Initiation of fluid removal</td>
<td>Ultrafiltration</td>
</tr>
<tr>
<td>Correction of volume overload</td>
<td>Diuretics (IV to Oral)</td>
</tr>
<tr>
<td>Initial adjustment of oral meds</td>
<td>D/C Vasodilators</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration</td>
</tr>
<tr>
<td>Further adjustment of oral meds</td>
<td>ACE-1, spironolactone, digoxin</td>
</tr>
<tr>
<td>Evaluation for potential interventions</td>
<td>Oral diuretics, ACE-I/ARB’s</td>
</tr>
<tr>
<td>including myocardial revascularization</td>
<td>Spironolactone, digoxin, BB’s, Nitrates/Hydralazine.</td>
</tr>
<tr>
<td></td>
<td>Myocardia Irevascularization</td>
</tr>
<tr>
<td></td>
<td>AICD, CRT, MV surgery, LV reconstruction, transplantation</td>
</tr>
</tbody>
</table>
Adhere Registry Disposition

All Enrolled Discharges (n=150,745) October 2001 to December 2004

- Home: 62%
- Hospice/LT Care: 15%
- Home with Add’l Care: 14%
- Deceased: 4%
- Inter-hospital Transfer: 3%
- Other/Unknown: 2%
- Outpatient Care: <1%
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HF Disease Management