HEART FAILURE BOARD REVIEW
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OBJECTIVES
- Scope of the problem: Epidemiology
- Acute Decompensated Heart Failure
- Management of Chronic Heart Failure with Reduced Ejection Fraction (HFrEF)
- Management of Chronic Heart Failure with Preserved EF (HFpEF)

EPIDEMIOLOGY
- 5.8 million people in the United States living with Heart Failure
  - 25% increase by 2030
  - 670,000 new diagnoses each year
  - Estimated total cost of care $39.2 billion
    - $20.9 billion in hospital costs
- 2.2 million in US with AIDS/HIV
  - 50,000 new cases annually
- 2.8 million in US with Breast CA
  - 295,240 new cases annually
- 2.9 million in US with Prostate CA
  - 220,800 new cases annually

EPIDEMIOLOGY
- The number is growing:
  - Revascularization of AMI
  - Increasing burdens of obesity, DM, HTN
  - The population is aging:
    - CHF is a disease of the elderly
    - Population > 65 yo will double in the next 20 years
    - 15% over 65 yo have heart failure
- 50% have preserved EF (HFpEF)
  - Heart failure clinically, but normal systolic function
  - Elderly, female, DM, HTN

ACUTE DECOMPENSATED HEART FAILURE

Major criteria:
- Paroxysmal nocturnal dyspnea
- Increased central venous pressure (>16 cm H2O at right atrium)
- Jugular venous distention
- Hepatomegaly
- Rales
- Cardomegaly on Chest xray
- Acute pulmonary edema
- S3 gallop
- Weight loss >4.5 kg in 5 days in response to treatment

Minor criteria:
- Bilateral lower extremity edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia (heart rate>120 beats/min)

FRAMINGHAM CRITERIA FOR CHF
- 2 major
- 1 major + 2 minor

Roger et al. Circulation 2011;123; e18-e209
In the general population of symptomatic heart failure patients, 50% of patients will be dead within 5 years of diagnosis.
ACC/AHA STAGES OF HEART FAILURE

- **Stage A**: At risk for HF but without structural heart disease or symptoms of HF.
- **Stage B**: Structural heart disease but without signs or symptoms of heart failure.
- **Stage C**: Structural heart disease with prior or current symptoms of heart failure.
- **Stage D**: Refractory heart failure requiring specialized interventions.

MANAGEMENT OF ACUTE HEART FAILURE

- Relieve symptoms
- Stabilize hemodynamics
- Identify and treat ‘trigger’

QUESTION

What is the most utilized class of medication to treat acute decompensated heart failure?

A. ACE-I  
B. Aldosterone Antagonists  
C. Loop Diuretics  
D. Beta Blockers

MOST UTILIZED DRUG TO TREAT HF?

Diuretics

- 90% of patients hospitalized for decompensated heart failure receive IV loop diuretics.
HOW MUCH?

[Image: Fractional Excretion of Sodium]


DOSE TRIAL

Felker GM et al, NEJM 2011

QUESTION

Loop diuretic therapy in heart failure has been shown to:

- A - Improve survival
- B - Reduce sudden cardiac death risk
- C - Reduce neuro-hormonal activation
- D - Causes worsening renal function

DIURETICS

- Symptom improvement
- No effect on survival documented (exception – Aldo Antagonist)
- Loop diuretics drug of choice
- Potentially harmful
  - Renal function
  - Electrolyte imbalance
  - Neurohormonal activation

MOST UTILIZED DRUG TO TREAT HF?

Diuretics

Vasodilators

Inotropes

Table 1: Secondary End Points for Each Treatment Comparison

<table>
<thead>
<tr>
<th>End Point</th>
<th>Continuous Infusion (N = 126)</th>
<th>P Value</th>
<th>Low Dose (N = 125)</th>
<th>P Value</th>
<th>High Dose (N = 127)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for diuresis at 72 hr</td>
<td>445.5 (161)</td>
<td>0.33</td>
<td>441.6 (152)</td>
<td>0.37</td>
<td>440.6 (145)</td>
<td>0.35</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr — no treatment vs (%)</td>
<td>20/153 (13)</td>
<td>0.04</td>
<td>36/148 (25)</td>
<td>0.02</td>
<td>50/150 (33)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in weight at 72 hr — lbs</td>
<td>-4.6 (0.3)</td>
<td>0.001</td>
<td>-4.8 (0.4)</td>
<td>0.001</td>
<td>-4.6 (0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — mL</td>
<td>-2315.3 (388)</td>
<td>0.001</td>
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<td>0.001</td>
<td>-2315.3 (388)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr — mg/L</td>
<td>-746 (494)</td>
<td>0.001</td>
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<td>0.001</td>
<td>-746 (494)</td>
<td>0.001</td>
</tr>
<tr>
<td>Worsening or persistent heart failure — %</td>
<td>31.8</td>
<td>0.43</td>
<td>20/147 (14)</td>
<td>0.06</td>
<td>22/134 (16)</td>
<td>0.06</td>
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<tr>
<td>Treatment Side Effects — %</td>
<td>54.6</td>
<td>0.04</td>
<td>50/147 (33)</td>
<td>0.64</td>
<td>50/147 (33)</td>
<td>0.64</td>
</tr>
<tr>
<td>Length of stay in hosp — days</td>
<td>5.5</td>
<td>0.03</td>
<td>5</td>
<td>0.35</td>
<td>6</td>
<td>0.35</td>
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<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3-8</td>
<td>3-8</td>
<td>4-6</td>
<td>3-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and out of hosp — days</td>
<td>51</td>
<td>0.39</td>
<td>39</td>
<td>0.52</td>
<td>40</td>
<td>0.52</td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
<td>39</td>
<td>40</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>40-52</td>
<td>38-55</td>
<td>39-54</td>
<td>40-56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2-2.5 x home dose of diuretic given in IV formulation
**ACUTE HEART FAILURE VASODILATOR RX**
- Nitroprusside
- Nitroglycerin
- Nesiritide
- Milrinone (ino-dilator)

**VASODILATOR THERAPY**

<table>
<thead>
<tr>
<th>HFpEF and HFpEF patients given sodium nitroprusside</th>
<th>Equivalent Decreases in PCWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF Ees = 3.66</td>
<td>DHF Ees = 6.94</td>
</tr>
<tr>
<td>HFpEF Ees = 6.94</td>
<td>DHF Ees = 0.64</td>
</tr>
</tbody>
</table>

Schwartzenberg and Borlaug, JACC, 2012

**RULE OUT CAD WHEN APPROPRIATE**
- Wall motion defects common in HF pts
- Coronary Angiography
  - Angina
  - Atypical CP, known or suspected CAD
- Non-invasive Stress Imaging
  - Known CAD w/o angina
  - To define likelihood of CAD

*Typically go directly to angiogram!*

**CHRONIC MANAGEMENT OF HEART FAILURE WITH REDUCED EJECTIONFRACTION**

**EFFECT OF ACE-I ON MORTALITY AND HOSPITALIZATIONS IN PATIENTS WITH HF**

- Total Mortality: -23
- Death or Hospitalization: -31
- CHF Hospitalization: -35

OR 0.77 (0.67-0.88) p<0.001

32 Trials of ACE in Heart Failure: ACEI (n = 3870), Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trials
JAMA 1995;273:1450-1456

**ACE INHIBITION IN HEART FAILURE**

*Consensus Recommendations*

- All patients with heart failure due to left ventricular systolic dysfunction should receive an ACE inhibitor unless they have a contraindication to its use or cannot tolerate treatment with the drug.
- This includes patients who have not developed HF symptoms but have a low EF.
MAJOR PLACEBO CONTROLLED TRIALS OF β-BLOCKADE IN HEART FAILURE

US Carvedilol Trials¹ (correlation of β blockade on in hospital mortality)

Mortality (%)

Carvedilol (n=2878)

Placebo (n=2938)

65% ↓
P<.001

MERIT-HF²

Mortality (%)

Merit-HF (n=5990)

Placebo (n=6060)

34% ↓
P=.0002

CIBIS-II³

Mortality (%)

Cibis-II (n=1094)

Placebo (n=1148)

34% ↓
P=.0007


2


3


TO BETA BLOCK OR NOT TO BETA BLOCK?

• Continue beta blocker while inpatient
• If not on a beta blocker
  • Start very low dose prior to discharge if euvoletic and able to tolerate
  • Only 3 beta blockers utilized in HFrEF
    • Toprol XL
    • Coreg
    • Bisoprolol

Bisoprolol (n=1327)

Placebo (n=1320)

CIBIS

P<.001

Survival

34%

EMPHASIS-HF: Eplerenone Effects in NYHA Class II Patients with LVEF ≤35%


RANDOMIZED ALDACTONE EVALUATION STUDY (RALES)

P=0.001

30% relative risk reduction

Randomized Aldactone Evaluation Study (RALES)

Placebo

Spironolactone


Aldosterone Receptor Blockers: Integrated Recommendations

Chronic heart failure (HFS) (2012 update)

Post MI HF (HFS)

Selected pts with moderate to severe symptoms and reduced LVEF who can be carefully monitored for preserved renal function and normal K concentration.

Not recommended:

- Creatinine > 2.5 mg/dl, or GFR <30 ml/min
- K < 3.0 mEq/L
- In conjunction with other potassium-sparing diuretics
- Calcium-sparing diuretics
- Concomitant use of CYP3A4 inhibitors (eplerenone)

Monitoring:

- Where monitoring K and renal function may not be feasible, risks may outweigh the benefits.
- Measure K, weight ≤10 lbs every 3 mos
- Do not give supplemental K unless <4.0 mEq/L ("persistently")
ISORDIL-HYDRAZINE

- VHEFT I (ISDN/HYD v. Prazosin v. placebo)
- VHEFT II (ISDN/HYD v. Enalapril v. placebo)
- AHEFT (ISDN/HYD v. Placebo)
- Decreased morbidity and mortality
  - Class I indication for African Americans
  - Class IIa indication for all others

DIGOXIN

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


NEW KIDS ON THE BLOCK

- PARADIGM-HF
- 8442 pts with EF ≤ 40%
  - Class II-IV
  - LCZ696 200mg BID - or -
  - Enalapril 10mg BID
- Primary outcome:
  - CV death or HF rehospitalization
  - LCZ696: more hypotension and mild angioedema
  - Enalapril: more renal impairment, hyperkalemia, and cough


IVABRADINE

- SHIFT – placebo controlled trial
- 6558 pts w/ EF ≤ 35%
  - Class II-IV
  - In NSR
  - On BB at time of enrollment
  - Ivabradine 7.5mg vs. placebo

Lancet 2010; 376: 875-85
QUESTION 2
In a patient with asymptomatic systolic heart failure which medication is not indicated

- A. ACE inhibitors
- B. Beta-blockers
- C. Digoxin
- D. Aldactone

DEVICE THERAPY

MADIT-II SURVIVAL RESULTS

Mortality by Intention-to-Treat

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone vs. Placebo</th>
<th>ICD Therapy vs. Placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.96</td>
<td>0.77</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.86, 1.30</td>
<td>0.62, 0.96</td>
<td>0.90</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.529</td>
<td>0.007</td>
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Bi-Ventricular Pacemakers

<table>
<thead>
<tr>
<th></th>
<th>Percentage of Patients Free of Death from Any Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac resynchronization</td>
</tr>
<tr>
<td></td>
<td>459</td>
</tr>
<tr>
<td></td>
<td>351</td>
</tr>
<tr>
<td></td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>8</td>
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</tbody>
</table>

No. 3

In which of the following patients is ICD indicated

- A – A patient with new onset HF who has a 3 beat run of NSVT
- B – A patient with stage D heart failure
- C – Long standing HF patient with an LVEF of 40%
- D – Long-standing HF pt with Class II symptoms with no hx of syncope
ACC/AHA GUIDELINES
Bi-Ventricular Pacemakers
Class I Indication
• LVEF ≤ 35%, sinus rhythm,
• NYHA Class III or ambulatory class IV symptoms despite recommended, optimal medical therapy
• cardiac dyssynchrony
• QRS duration > 0.12ms

Circ 2005;112:1825-1852

ACC/AHA
Placement of an AICD is reasonable in patients with an LVEF of 30-35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy who have reasonable expectation of survival with good functional status of more than one year.

Class Ia indication

Circ 2005;112:1825-1852

CONCLUSIONS
• Heart failure is a chronic, progressive disease that is generally not curable, but manageable.
• The prognosis with heart failure with reduced ejection fraction (HFrEF) has improved with both advances in medications and devices
• There are no treatment options for heart failure with preserved ejection fraction (HFpEF) that are known to definitively improve morbidity and mortality
• Management is based on risk factor modification

OVERVIEW OFDEVICE THERAPY
FOR HEART FAILURE

CHARM-Preserved
Primary Endpoint

HR 0.89 (95% CI 0.77-1.03), P=0.118
Adjusted HR 0.86, P=0.051

CV death or HF hospitalization (%)

11% risk reduction

Placebo
Candesartan

Number at risk:
Candesartan 1514
Placebo 1509

Time (years)
0 1 2 3 3.5

TOPCAT
• 3445 heart-failure patients >50 yo with an LVEF >45% at 270 sites in six countries
• aldosterone antagonist (aldactone) vs placebo
• no benefit on primary end-point
• significantly fewer CHF hospitalizations over the average follow-up of 3.3 years

NON-PHARMACOLOGIC MANAGEMENT OF HEART FAILURE
- Determine etiology of decompensation and treat
  - Rule-out CAD
  - Rate/Rhythm management
  - Sodium restriction
  - Fluid restriction
  - CPAP if indicated
  - Stop smoking
  - Limit EtOH
  - Avoid NSAIDS
  - Exercise

CPAP IN HEART FAILURE
- Helps decrease preload and afterload
  - Decreased mortality and decreased need for cardiac transplantation
    - Allows heart to “rest”
    - Improved CO
    - Improved outcomes and cardiac function
    - Decreased BP and HR
    - Decreased neurohormonal levels

AVOID NSAIDS
- Decreased prostaglandin synthesis by Cox inhibition
  - Alters cardiovascular and renal homeostasis
    - Decreased afferent arteriole vasodilation
    - Increased ANG II functionality
    - Increase total body sodium and water
    - Increased fluid retention
    - Worsening heart failure

EXERCISE
- Exercise training is beneficial in heart failure
  - Improved exercise tolerance and duration with training
  - Improved ventilatory response
  - Improved endothelial function and perfusion to skeletal muscles
  - > 30% reduction in morbidity and mortality

Circulation. 2003; 107: 1210-1225

Circulation. 2000; 102: 61-66
Heart Dis. 2002 Mar-Apr;4(2):102-9
CONCLUSIONS

• ACE Inhibitors/ARB’s, Beta Blockers, and Aldosterone antagonists have been shown to decrease mortality.

• Device therapy with BiV pacemakers and AICD’s (in appropriate patients) have also been shown to decrease mortality.

• Device therapy is now a Class I indication in appropriate patients.