MEDICAL MANAGEMENT OF PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

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OVERVIEW

• What are the ACC/AHA Stages of HF?
• What are the NYHA Classes of HF
• How do we relate these stages and classes to medical tx?
• A Closer look at each Stage with focus on evidence
• A Closer look at the Drugs we use everyday in HF with special attention to side effects
ACC/AHA STAGES OF HEART FAILURE

ACC/AHA STAGES OF HEART FAILURE

- Stage A: High risk with no symptoms
- Stage B: Structural heart disease, no symptoms
- Stage C: Structural disease, previous or current symptoms
- Stage D: Refractory symptoms requiring special intervention

A 52 yo male with history of HTN. He has no SOB or CP. Screening ECHO does not show structural disease such as LVH. What Stage HF is he?

- A. Stage A
- B. Stage B
- C. Stage C
- D. Stage D
# New York Heart Association (NYHA) Classification of Cardiac Disease

<table>
<thead>
<tr>
<th>Functional Capacity</th>
<th>Objective Assessment</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.</td>
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<tr>
<td>Class II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
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<tr>
<td>Class III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
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<tr>
<td>Class IV</td>
<td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present, even at rest. If any physical activity is undertaken, discomfort is increased.</td>
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</table>

• A 76 year old woman with history of MI and ischemic cardiomyopathy EF 30% has SOB at rest despite taking her prescribed medications. She is
  • A. ACC/AHA Stage A NYHA Class I
  • B. ACC/AHA Stage B NYHA Class II
  • C. ACC/AHA Stage C NYHA Class III
  • D. ACC/AHA Stage D NYHA Class IV
<table>
<thead>
<tr>
<th>Indication</th>
<th>ACE inhibitor</th>
<th>Angiotensin Receptor Blocker</th>
<th>Diuretic</th>
<th>Beta Blocker</th>
<th>Aldosterone Antagonist</th>
<th>Cardiac Glycoside</th>
<th>CRT</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic LV dysfunction (NYHA Class I)</td>
<td>Indicated</td>
<td>If ACE intolerant</td>
<td>Not indicated</td>
<td>Post-MI Indicated*</td>
<td>Recent MI</td>
<td>With atrial fibrillation</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Symptomatic HF (NYHA Class II)</td>
<td>Indicated</td>
<td>Indicated with or without ACE inhibitor</td>
<td>Indicated if fluid retention</td>
<td>Indicated</td>
<td>Recent MI</td>
<td>1. With atrial fibrillation 2. When improved from more severe HF in sinus rhythm</td>
<td>Not indicated</td>
<td>Indicated</td>
</tr>
<tr>
<td>Worsening HF (NYHA Class III or IV)</td>
<td>Indicated</td>
<td>Indicated with or without ACE inhibitor</td>
<td>Indicated, combination of diuretics</td>
<td>Indicated (under specialist’s care)</td>
<td>Indicated</td>
<td>Indicated if QRS &gt;0.12†</td>
<td>Indicated</td>
<td>Indicated</td>
</tr>
<tr>
<td>End-stage HF (NYHA Class IV)</td>
<td>Indicated</td>
<td>Indicated with or without ACE inhibitor</td>
<td>Indicated, combination of diuretics</td>
<td>Indicated (under specialist’s care)</td>
<td>Indicated</td>
<td>Indicated if QRS &gt;0.12†</td>
<td>Indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

*Represents expert opinion. Patients must be in sinus rhythm.
†May be indicated in some patients with a prolonged life expectancy.
CE = angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association.

STAGE A HEART FAILURE

• Pts at high risk for heart failure
• 75% of cases have antecedent hypertension
• Diabetics with blood sugar >300mg% are three times as likely to develop heart failure
• Focus on this groups is prevention and treating risk factors for heart disease
STAGE B HEART FAILURE

• Evidence of Structural Heart disease without sx

• Evidence is limited

• Much of the treatment is extrapolated from evidence from symptomatic HF

• SOLVD Long term followup demonstrates mortality benefit with asymptomatic patients on enalapril
TREATING THE STAGE B HEART FAILURE PATIENT

• SAVE Trial:

• 2231 patients 3 days post MI without HF and EF <40%

• Randomized to captopril vs. placebo

• EF fell 9% in placebo group

• 19% reduction in all cause mortality and 22% reduction in heart failure hospitalization
SAVE TRIAL COMBINATION THERAPY

• Patients who received a combination of ACEi and β-blockers had the lowest mortality.
STAGE C HEART FAILURE

• Pts with structural Heart disease and current or past symptoms of heart failure
• Focus on treatment is inclusion of ACEi and β-blockers
• Addition of diuretics and digoxin
• Addition of aldosterone or nesiritide
• Revascularization, valve surgery considered
• Multidisciplinary approach
• Sodium restriction
STAGE D HEART FAILURE

- Structural Heart disease with symptoms despite maximal medical tx requiring special interventions
  - Inotropes
  - ICDs, CRT, VADs, transplantation
  - hospice
ACE INHIBITORS KEY POINTS

• Start low, titrate to evidence based doses
• Check K+ 1-2 weeks post titration
• Minimize concomitant ASA use
• Watch for side effects, hyperkalemia
• Do note use for bilateral RAS, K>5.5
BETA BLOCKERS

- Bisoprolol, Carvedilol, and Metoprolol Succinate have been shown to improve mortality
- Start at low dose and slowly uptitrate
- Caution in hypotension or volume depletion
- Relative contraindications include RAS, asymptomatic bradycardia, DM with hypoglycemia and resting limb ischemia
• Which of the following beta blockers has not been shown to improve mortality in HF?
  
  • A. bisoprolol
  • B. atenolol
  • C. metoprolol succinate
  • D. carvedilol
UNANSWERED QUESTIONS

• What to do about the acute heart failure decompensation and beta blockers?
DIGITALIS?

• The DIG trial
• No difference in pts with HF in overall mortality
• Trend towards better outcomes in worsening HF mortality
• Definite reduction in cardiovascular hospitalization or for HF related hospitalization
• Increased risk may be associated with increased dig levels (>1.2)
# Mortality and Hospitalization in the DIG Trial

<table>
<thead>
<tr>
<th></th>
<th>Digoxin (n=3,397)</th>
<th>Placebo (n=3,403)</th>
<th>Risk Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall mortality</strong></td>
<td>1,181 (34.8)</td>
<td>1,194 (35.1)</td>
<td>0.99 (0.91 to 1.07)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Death due to worsening heart failure</strong></td>
<td>394 (11.6)</td>
<td>449 (13.2)</td>
<td>0.88 (0.77 to 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Hospitalization-cardiovascular</strong></td>
<td>1,694 (49.9)</td>
<td>1,850 (54.4)</td>
<td>0.87 (0.81 to 0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hospitalization for worsening heart failure</strong></td>
<td>910 (26.8)</td>
<td>1,180 (34.7)</td>
<td>0.72 (0.66 to 0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cl=confidence interval
DIG: TAKING ANOTHER LOOK?

• Equal overall mortality was attributed to patients with dig levels greater than 1.2...

• Lower levels of dig might improve mortality
MINERALOCORTICOID RECEPTOR ANTAGONISTS

• Spironilactone blocks the effects of aldosterone, reducing salt and water retention by decreasing H+ and K+ excretion by the kidneys
RALES TRIAL

• RALES trial randomized NYHA III-IV HF LVEF <35% patients on background medical therapy to aldactone vs. placebo

• Primary endpoint was all cause mortality

• 30% reduction in death (P=0.001)
CUMULATIVE INCIDENCE (%)

- Placebo
- Eplerenone

\[
P = 0.008 \\
\text{RR} = 0.85 \ (95\% \ CI, \ 0.75-0.96)
\]

SIDE EFFECTS OF THE MINERALOCORTICOID RECEPTOR ANTAGONISTS

• Hyperkalemia

• Antiandrogenic and progesterone-like effects
  • Gynecomastia in men
  • Impotence
  • Menstrual irregularities
DIURETICS

- In short term trials, diuretics have been shown to decrease
  - jugulovenous pressures
  - Pulmonary congestion
  - Peripheral edema
  - Body weight
DIURETICS

• In intermediate term studies, diuretics have been found to improve cardiac function, symptoms and exercise tolerance

• To date, there have been no long-term studies on diuretics in heart failure, therefore their effects on morbidity and mortality are unknown.
DIURETICS IN ACUTE HF

• If there is significant volume overload, or diuretic resistance, continuous intravenous infusion should be considered. (Lasix 5-40mg/hr)
  • Less compensatory Na retention
  • Less renal dysfunction
  • Less ototoxicity
  • Less gout
  • Hypotension
  • Gastrointestinal complaints
DIURETIC DRIPS

• A meta-analysis of two trials using continuous infusion drips demonstrated a 48% reduction in all cause mortality

• Salvador et al Cochrane Review 2005
DIURETICS: A NECESSARY EVIL

• Worsening renal failure and survival based on
• Worsening LVF in chronic HF in animal models
• Electrolyte disorders
  • Hyponatremia
  • Hypokalemia
  • hypomagnesemia
NITRATES & HYDRALAZINE TRIAL

• Potent vasodilators, producing rapid decreases in pulmonary venous pressures and ventricular pressured and reducing congestion

• At moderate doses, nitrates act as arteriolar vasodilators reducing afterload and increasing cardiac output

• Problem is tachyphylaxis, an dosing

• Findings from Va-HeFT and A-HeFT trial suggest use may be beneficial in specific ethnic populations (African Americans)
DOBUTAMINE

- The most widely prescribed inotrope despite evidence that it increases mortality
- Improves cardiac output through inotropy and chronotropy
- Improves renal perfusion at low doses (1-2 μg/kg/min)
- Higher doses (10-20 μg/kg/min) may be necessary for hypotension
DOBUTAMINE: WHAT IS THE EVIDENCE?

- CASINO
  - Calcium Sensitizer or Inotrope or None
  - Demonstrated a 42% mortality at 6 mon with patients treated with 10 mg/kg/min infusions of dobutamine versus 28.3% in placebo in patients with acute HF
  - Other studies have demonstrated same in chronic HF and confirmed results in acute Hf.
WHERE WE’VE BEEN

• Definitely literature supports use of several medications for acute and chronic HF, but all with certain caveats

• There is no free lunch

• Remember the ACC/AHA Stages and NYHA Classes when stratifying patients

• References: Braunwald 8th edition, Libby et al. pg583-640; Mayo Cardiovascular Board Review 2008, AHA/ACC 2013 Heart Failure Guidelines, Yancy et al