

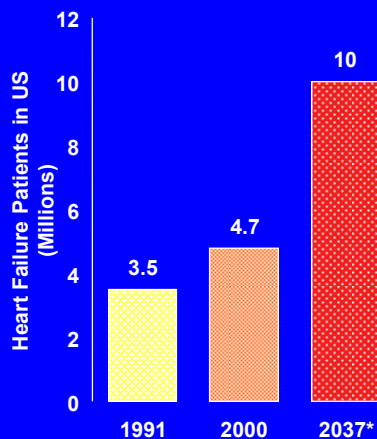
# PHARMACOTHERAPY OF HEART FAILURE

**BY**

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**MD CARDIOLOGY**

## Heart Failure *A Growing Epidemic*



- 4.7 million symptomatic patients, estimated 10 million in 2037
- Incidence: About 550,000 new cases/year
- More deaths from heart failure than from all forms of cancer combined
  - 53,000 deaths a year
- Prevalence is 1% between the ages of 50 and 59, progressively increasing to >10% over age 80
- ~ \$30 billion/year (5% to 7% of total health care cost)

\*Rich M. *J Am Geriatric Soc.* 1997;45:968-974.  
American Heart Association. 2001 *Heart and Stroke Statistical Update.*

## Classification Systems

- |   |  |  |
|---|--|--|
| <ul style="list-style-type: none"> <li>• NYHA based on exercise capacity (functional system)             <ul style="list-style-type: none"> <li>– Class I</li> <li>– Class II</li> <li>– Class III</li> <li>– Class IV</li> </ul> </li> </ul> |  | <ul style="list-style-type: none"> <li>• ACC/AHA staging of heart failure (progression)             <ul style="list-style-type: none"> <li>– Stage A</li> <li>– Stage B</li> <li>– Stage C</li> <li>– Stage D</li> </ul> </li> </ul> |
|---|--|--|

## New Approach to the Classification of Heart Failure

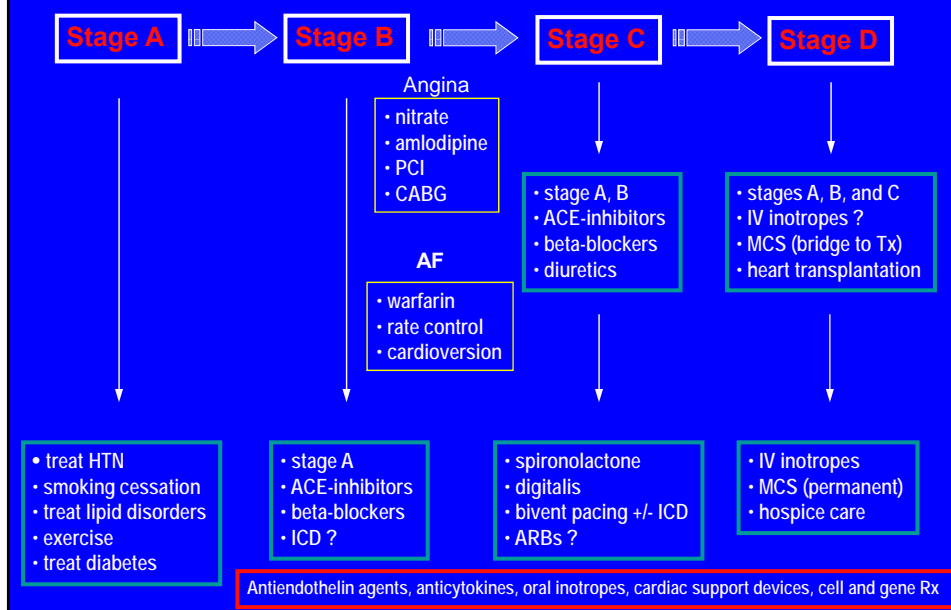
	Stage	Patient Description
<b>A</b>	•High risk for developing heart failure (HF)	<ul style="list-style-type: none"> <li>• Hypertension</li> <li>• CAD</li> <li>• Diabetes mellitus</li> <li>• Family history of cardiomyopathy</li> </ul>
<b>B</b>	•Asymptomatic HF	<ul style="list-style-type: none"> <li>• Previous MI</li> <li>• LV systolic dysfunction, LVH</li> <li>• Asymptomatic valvular disease</li> </ul>
<b>C</b>	•Symptomatic HF	<ul style="list-style-type: none"> <li>• Known structural heart disease</li> <li>• Shortness of breath and fatigue</li> <li>• Reduced exercise tolerance</li> </ul>
<b>D</b>	•Refractory end-stage HF	<ul style="list-style-type: none"> <li>• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized)</li> </ul>

Modified from Hunt SA et al. J Am Coll Cardiol. 2001;38:2101–2113.

## Classification of HF

- Which side of heart is affected
  - Left (more common)
  - Right (right-sided MI, pulmonary HTN)
- Which heart function is affected
  - Systolic ( $\downarrow$  contraction and EF, dilated LV)
  - Diastolic ( $\downarrow$  relaxation,)
    - Failure of LV filling
    - Contractile function and EF usually normal

## 2006 HF Treatment Algorithm by Stage



## The case of Mr. Jones

- 32 y/o AA male presents with progressive DOE over the past 3 weeks - unable to walk one flight of stairs without resting. He also complains of severe weight gain over this time period (>15 lbs), feeling bloated, and unable to sleep because he feels like he stops breathing.
- PE: HR 110s, BP 115/75
- JVD to jaw, pitting edema



## What to do with Mr. Jones?

- What studies do you want to order?
- What medication first?
  - ACE-I vs. beta blocker
  - Which ACE-I? Which beta blocker?
- Can I start a beta blocker with bad CHF?
- When to start diuretics?

## ACE-inhibitors

- First-line treatment
- Beneficial across all functional classes of HF
- Reduce risk of developing HF in at-risk patients (ALVD, previous MI, > 55 y.o. with vascular disease or DM)
- Start low, titrate to target (doses shown effective in clinical trials)

### ACE Inhibitors in Heart Failure: From Asymptomatic LVD to Severe HF

#### SOLVD Prevention (Asymptomatic LVD)

20% ↓ death or HF hosp.

29% ↓ death or new HF

#### SOLVD Treatment (Chronic Heart Failure)

16% ↓ mortality

#### CONSENSUS (Severe Heart Failure)

40% ↓ mortality at 6 mos.

31% ↓ mortality at 1 year

27% ↓ mortality at end of study

- No difference in incidence of sudden cardiac death

SOLVD Investigators. N Engl J Med 1992;327:685-91.  
 SOLVD Investigators. N Engl J Med 1991;325:293-302.  
 CONSENSUS Study Trial Group. N Engl J Med 1987;316:1429-35.

## Beta blockers

- Historically contraindicated, but strong evidence now refutes that
- Standard therapy in HF
- Class effect – most studies with carvedilol and metoprolol
- Start when euvolemic and stable
- Start low and titrate to max tolerated

## Effect of Beta Blockade on Outcome in Patients With HF and Post-MI LVD

Study	Drug	HF Severity	Target Dose (mg)	Outcome
US Carvedilol <sup>1</sup>	carvedilol	mild/moderate	6.25-25 BID	↓ 48% disease progression (p= .007)
CIBIS-II <sup>2</sup>	bisoprolol	moderate/severe	10 QD	↓ 34% mortality (p < .0001)
MERIT-HF <sup>3</sup>	metoprolol succinate	mild/moderate	200 QD	↓ 34% mortality (p = .0062)
COPERNICUS <sup>4</sup>	carvedilol	severe	25 BID	↓ 35% mortality (p = .0014)
CAPRICORN <sup>5</sup>	carvedilol	post-MI LVD	25 BID	↓ 23% mortality (p = .031)

1. Colucci WS et al. Circulation 1196;94:2800-6.

2. CIBIS II Investigators. Lancet 1999;353:9-13.

3. MERIT-HF Study Group. Lancet 1999;353:2001-7.

4. Packer M et al. N Engl J Med 2001;344:1651-8.

5. The CAPRICORN Investigators. Lancet 2001;357:1385-90.

HFSA 2006 Practice Guideline	
Pharmacologic Therapy: Beta Blocker Overview*	
<b>General considerations</b>	Initiate at low doses
	Up-titrate gradually, generally no sooner than at 2 week intervals
	Use target doses shown to be effective in clinical trials
	Aim to achieve target dose in 8-12 weeks
	Maintain at maximum tolerated dose
<b>If symptoms worsen or other side effects appear</b>	Adjust dose of diuretic or concomitant vasoactive med.
	Continue titration to target after symptoms return to baseline
<b>If up-titration continues to be difficult</b>	Prolong titration interval
	Reduce target dose
	Consider referral to a HF specialist

**\* Consult language of specific recommendations**

Heart Failure Society of America

Adapted from: Adams KF, Lindenfeld J, et al. HFSA 2006 Comprehensive Heart Failure Guideline. J Card Fail 2006;12:e1-e122.

## Implications of CARMEN

- **First trial comparing BB monotherapy to ACEI monotherapy**
  - Beta blockers by themselves good enough
  - Good alternative in ACE-I intolerant patients
  - Combination therapy is likely best
- **Consensus supports ACE-I first, if tolerant**

## Back to Mr. Jones...

- Echocardiogram
  - EF 10-20%, global hypokinesis
  - Idiopathic dilated cardiomyopathy
- Carvedilol 3.125mg bid
- Lisinopril 5mg daily
- Lasix 40mg IV BID due to his LE edema
  
- Mr. Jones now has a dry cough and is uncomfortable
- Now what?



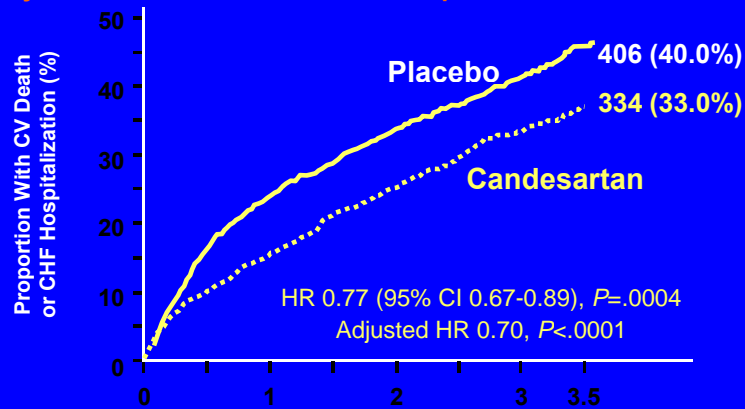
### HFSA 2006 Practice Guideline (7.10) Pharmacologic Therapy: Angiotensin Receptor Blockers

**ARBs are recommended** for routine administration to symptomatic and asymptomatic patients with an LVEF  $\leq$  40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency.

*Strength of Evidence = A*

## CHARM-Alternative

Primary outcome of CV death or CHF hospitalization

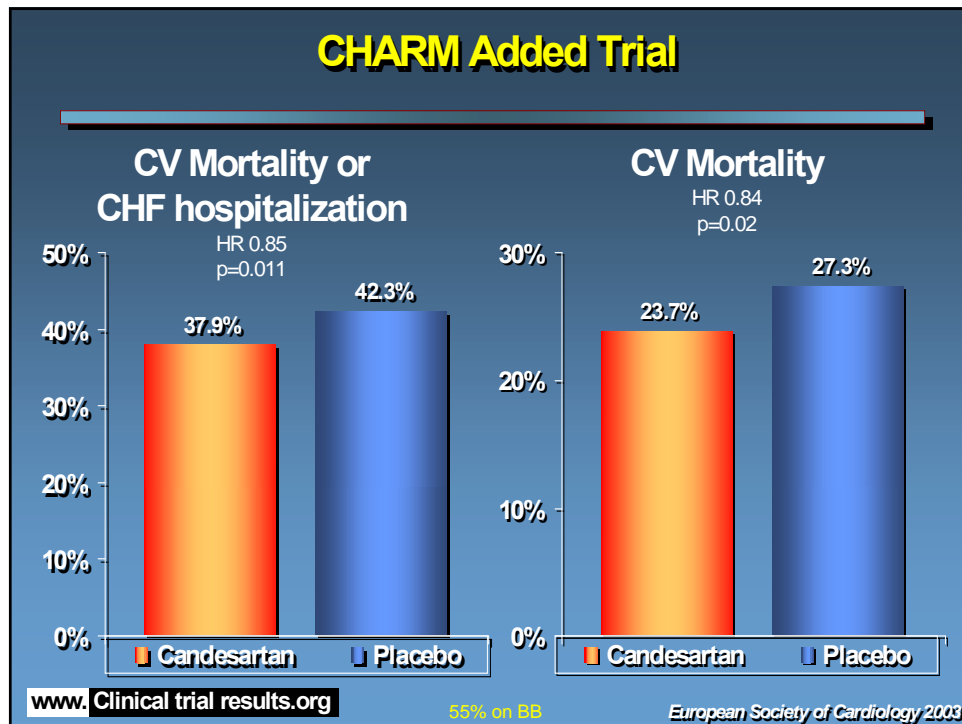


Number at risk	Years				
	0	1	2	3	3.5
Candesartan	1,013	929	831	434	122
Placebo	1,015	887	798	427	126

Granger CB, et al. *Lancet*. 2003;362:772-776.

## ACE/ARB combination

- What if Mr. Jones tolerated the ACE Inhibitor, would it be helpful or harmful add an ARB to his medications?
- BP 100/80 HR 72 Cr 1.1 K+ 4.1



## Poor Mr. Jones...

- Titrated up meds
  - Carvedilol 6.25 mg bid
  - Lisinopril 20 mg daily
  - Lasix 80 mg bid
- Still NYHA class III, tired of your continued failure to make him better
- Now what?



HFSA 2006 Practice Guideline (7.14-7.15)

## Pharmacologic Therapy: Aldosterone Antagonists

An aldosterone antagonist **is recommended** for patients on standard therapy, including diuretics, who have:

- NYHA class IV HF (or class III, previously class IV) due to LV systolic dysfunction ( $LVEF \leq 35\%$ )

One **should be considered** in patients post-MI with clinical HF or diabetes and an  $LVEF < 40\%$  who are on standard therapy, including an ACE inhibitor or an ARB.

*Strength of Evidence = A*

Heart Failure Society  
of America

Adapted from: Adams KF, Lindenfeld J, et al. HFSA 2006 Comprehensive Heart Failure Guideline. J Card Fail 2006;12:e1-e122.

## Hail to thee, polypharmacy...

*So, Mr. Jones is now taking:*

- Coreg 6.25mg bid
- Lisinopril 20mg daily
- Spironolactone 25mg qd
- Lasix 80mg bid
- His BP and HR still stable but had to D/C spironolactone due to severe increase K+
- He is still NYHA Class III
- Any other medications we can add?



HFSA 2006 Practice Guideline (7.19)  
**Pharmacologic Therapy:  
 Hydralazine and Oral Nitrates**

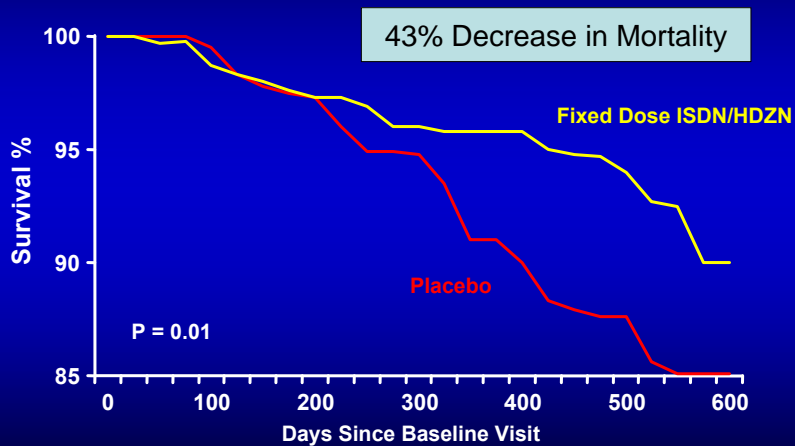
A combination of hydralazine and isosorbide dinitrate **is recommended** as part of standard therapy, in addition to beta-blockers and ACE-inhibitors, for African Americans with LV systolic dysfunction:

- NYHA III or IV HF      *Strength of Evidence = A*
- NYHA II HF              *Strength of Evidence = B*



Adams KF, Lindenfeld J, et al. HFSA 2006 Comprehensive Heart Failure Guideline. J Card Fail 2006;12:e1-e122.

**A-HeFT All-Cause Mortality**



Taylor AL et al. N Engl J Med 2004;351:2049-57.

## How did Mr. Jones do?

- Mr. Jones was discharged last week in NYHA class II heart failure, but comes back to the ED after gaining 10 lbs with an increase in fatigue and SOB – he's having trouble walking up one flight of stairs again.
- BP 95/52 HR 58 Cr 1.5 K+ 3.9
- What happened?
- Which meds should we hold?
- Should we change anything else?

## Diet and nutrition in HF

- Sodium restriction (2-3g/day) in all patients with clinical HF
- Fluid intake < 2 liters in patients with fluid retention and hyponatremia
- Consider daily MVI supplementation
- Caloric assessment / supplementation in patients with advanced HF/cachexia

## HFSA 2006 Practice Guideline (7.24) Pharmacologic Therapy: Diuretics

- Restoration of normal volume status may require multiple adjustments.
- Once a diuretic effect is achieved with short-acting loop diuretics, increase frequency to 2-3 times a day if necessary, rather than increasing a single dose. *Strength of Evidence = B*
- Oral torsemide **may be considered** in patients exhibiting poor absorption of oral medication or erratic diuretic effect. *Strength of Evidence = C*
- IV administration of diuretics may be necessary. *Strength of Evidence = A*
- Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying dysfunction.

## Digoxin

- Limited role in HF
- Does not improve mortality in mild to moderate HF
- Can reduce hospitalization in poorly controlled patients
- Narrow therapeutic window (0.125-0.250 mg daily)
- Watch for digoxin toxicity



## HFSA 2006 Practice Guideline

### Digoxin

#### *Recommendation 7.29*

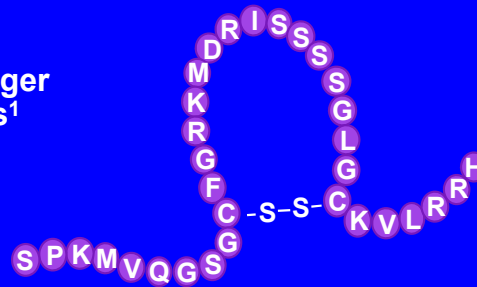
Digoxin **should be considered** for patients with LV systolic dysfunction (LVEF  $\leq$  40) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:

- NYHA class II-III      *Strength of Evidence = A*
- NYHA class IV        *Strength of Evidence = B*

## Mr. Jones redux

- You started IV lasix 80mg TID and Mr. Jones is not responding – urine output  $<$  1L a day
- Symptoms worsen to NYHA Class IV
- JVD to earlobes, bilateral rales
- Vital signs 95/50 HR 103
- Cr still 1.5 K+ stable
- Any suggestions?

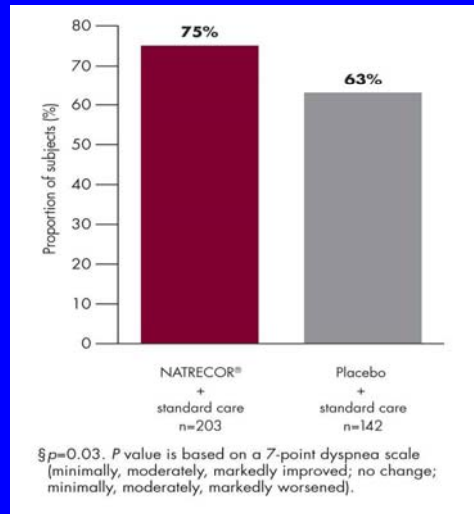
- NATRECOR® (nesiritide) has the same 32 amino acid sequence as the endogenous peptide<sup>1</sup>
- Human BNP increases intracellular cGMP, which serves as second messenger to dilate veins and arteries<sup>1</sup>
- Systemic Hemodynamic Effects<sup>1,2,3</sup>
  - preload and afterload reduction
  - increased cardiac index
  - no significant increase in heart rate



References: 1. NATRECOR® Full Prescribing Information.  
 2. Colucci WE et al. *N Engl J Med.* 2000;343:246  
 3. Abraham WT et al. *J Card Fail.* 1998;4:37

## Nesiritide Efficacy: Dyspnea Improvement in VMAC Trial

Significant improvement<sup>§</sup> in patient-reported dyspnea at 3 hours



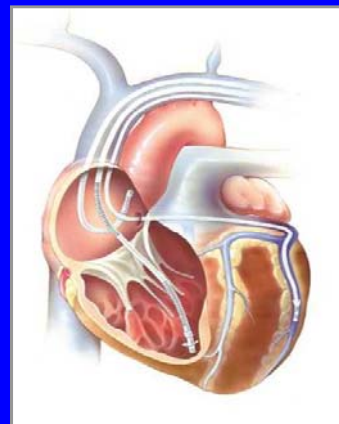
Reference: NATRECOR® Full Prescribing Information.

## Acute Decompensated Heart Failure: Nesiritide and Mortality

- No short-term therapy for ADHF has been proven to improve short- or long-term mortality rates.
- Nesiritide is the only approved ADHF therapy which has been shown in large, randomized trials to provide **both** significant symptomatic **and** hemodynamic improvement when added to standard care.
- Nesiritide has not been studied in a trial powered to evaluate an effect on mortality.
- Follow dosing instructions and patient exclusion criteria carefully

## Other last-ditch options

- Cardiac resynchronization therapy (CRT)
- Biventricular pacing
- ICD placement



**THANK YOU**

