

Congestive Heart Failure

Quality Assurance Training for Rural Hospitals

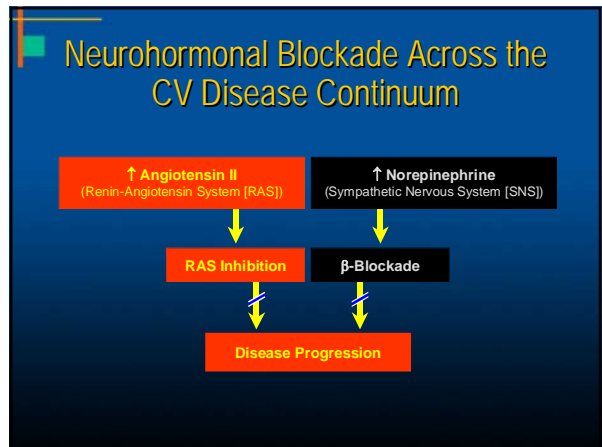
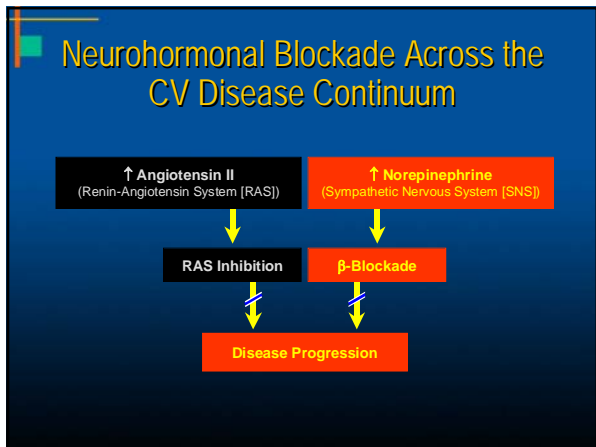
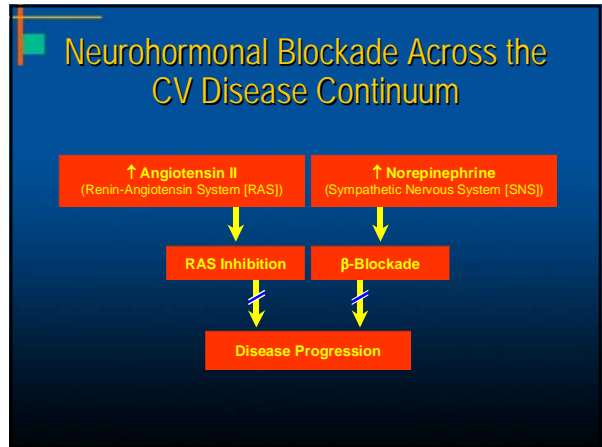
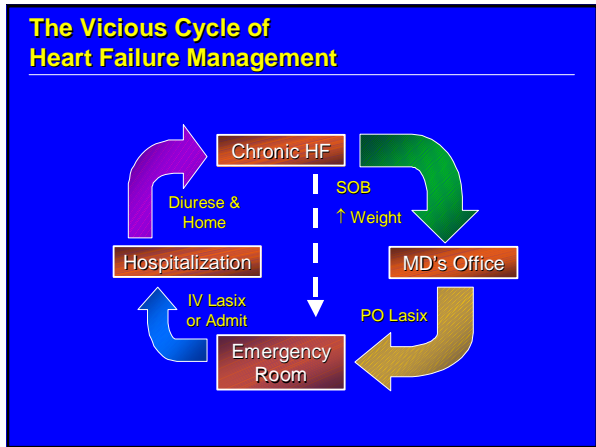
Optimal Management of Congestive Heart Failure in 2004

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Therapies for CHF

1. Medical Therapy
2. Cardiac Resynchronization Therapy
3. Sudden Cardiac Death Prevention
 - Suppression of the renin angiotensin aldosterone pathway and the sympathetic nervous system
 - ICD Therapy



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General Measures

| | |
|--|---|
| <p>Lifestyle Modifications:</p> <ul style="list-style-type: none"> • Weight reduction • Discontinue smoking • Avoid alcohol and other cardiotoxic substances • Exercise | <p>Medical Considerations:</p> <ul style="list-style-type: none"> • Treat HTN, hyperlipidemia, diabetes, arrhythmias • Coronary revascularization • Anticoagulation • Immunization • Sodium restriction • Daily weights • Close outpatient monitoring |
|--|---|

Pharmacologic Management

Digoxin

- Enhances inotropy of cardiac muscle
- Reduces activation of SNS and RAAS
- Controlled trials have shown long-term digoxin therapy:
 - Reduces symptoms
 - Increases exercise tolerance
 - Improves hemodynamics
 - Decreases risk of HF progression
 - Reduces hospitalization rates for decompensated HF
 - Does not improve survival

Pharmacologic Management

Diuretics

- Used to relieve fluid retention
- Improve exercise tolerance
- Facilitate the use of other drugs indicated for heart failure
- Patients can be taught to adjust their diuretic dose based on changes in body weight
- Electrolyte depletion a frequent complication
- Should never be used alone to treat heart failure
- Higher doses of diuretics are associated with increased mortality

Pharmacologic Management

ACE Inhibitors

- Blocks the conversion of angiotensin I to angiotensin II; prevents functional deterioration
- Recommended for all heart failure patients
- Relieves symptoms and improves exercise tolerance
- Reduces risk of death and decreases disease progression
- Benefits may not be apparent for 1-2 months after initiation

Effect of ACE Inhibitors on Mortality Reduction in Patients With LVD or Heart Failure

| Trial | Mortality | | RR (95% CI) |
|--------------------|------------|------------|------------------|
| | ACEI | Controls | |
| Chronic CHF | | | |
| CONSENSUS I | 39% | 54% | 0.56 (0.34–0.91) |
| SOLVD (Treatment) | 35% | 40% | 0.82 (0.70–0.97) |
| SOLVD (Prevention) | 15% | 16% | 0.92 (0.79–1.08) |
| Post MI | | | |
| SAVE | 20% | 25% | 0.81 (0.68–0.97) |
| AIRE | 17% | 23% | 0.73 (0.60–0.89) |
| TRACE | 35% | 42% | 0.78 (0.67–0.91) |
| SMILE | 6.5% | 8.3% | 0.78 (0.52–1.12) |
| Average | 21% | 25% | |

Garg R et al. JAMA. 1995;273:1450–1456.

Pharmacologic Management

Beta-Blockers

- Cardioprotective effects due to blockade of excessive SNS stimulation
- In the short-term, beta blocker decreases myocardial contractility; increase in EF after 1-3 months of use
- Long-term, placebo-controlled trials have shown symptomatic improvement in patients treated with certain beta-blockers¹
- When combined with conventional HF therapy, beta-blockers reduce the combined risk of morbidity and mortality, or disease progression¹

1 Hunt, SA, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001 p. 20.

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Effect of β -Blockade on Outcome in Patients With Heart Failure and Post-MI LVD

| Study | Drug | HF Severity | Target Dosage (mg/day) | Outcome |
|----------------------------|----------------------|-----------------|------------------------|--|
| US Carvedilol ¹ | carvedilol | mild/moderate | 6.25 to 25 bid | ↓48% disease progression ¹ (P=.001) |
| CIBIS-II ² | bisoprolol | moderate/severe | 10 qd | ↓34% mortality (P<.0001) |
| MERIT-HF ³ | metoprolol succinate | mild/moderate | 200 qd | ↓34% mortality (P=.0062) |
| COPERNICUS ⁴ | carvedilol | severe | 25 bid | ↓35% mortality (P=.0014) |
| CAPRICORN ⁵ | carvedilol | Post-MI LVD | 25 bid | ↓23% mortality (P=.031) |

¹Colucci WS et al. Circulation. 1996;94:2800-2806.
²CIBIS II Investigators and Committees. Lancet. 1999;353:9-13.
³MERIT-HF Study Group. Lancet. 1999;353:2001-2007.
⁴Packer M et al. N Engl J Med. 2001;344:1651-1659.
⁵The CAPRICORN Investigators. Lancet. 2001;357:1385-1390.

- ### Pharmacologic Management
- #### Aldosterone Antagonists
- Generally well-tolerated
 - Shown to reduce heart failure-related morbidity and mortality
 - Generally reserved for patients with NYHA Class III-IV HF
 - Side effects include hyperkalemia and gynecomastia. Potassium and creatinine levels should be closely monitored

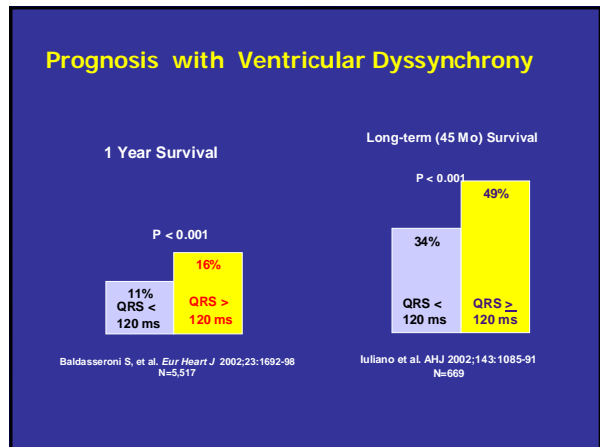
Trials with Aldosterone Blockade

Primary Endpoint: All-Cause Mortality

| | Placebo | Aldosterone Blockade | Hazard Ratio | Log-rank P-Value |
|---------|----------|----------------------|---------------------|------------------|
| EPHESUS | 554/3319 | 478/3313 | 0.85 (0.75,0.96) | 0.008 |
| RALES | 386/841 | 284/822 | 0.70 (0.60,0.82) | < 0.001 |

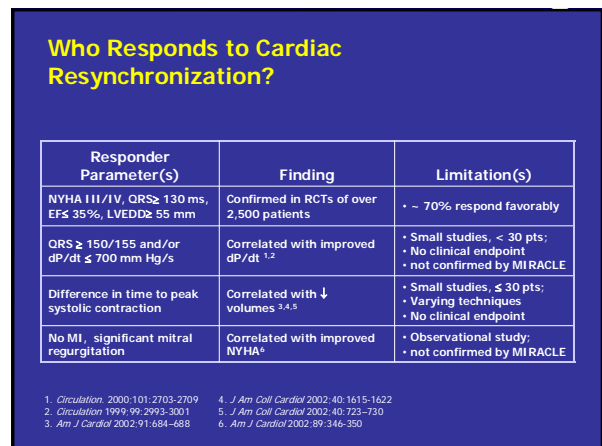
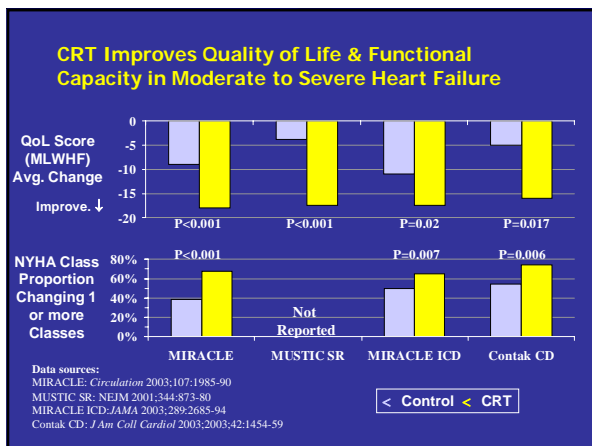
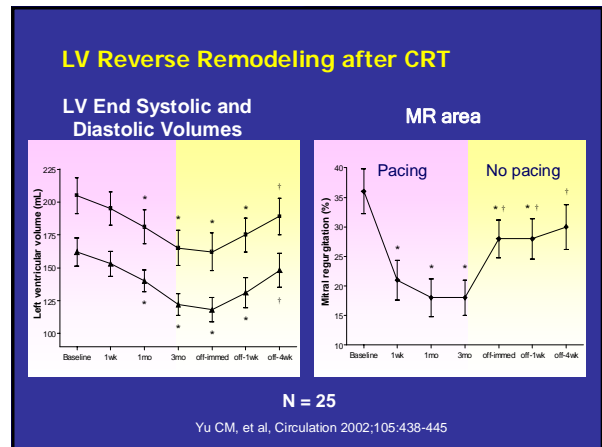
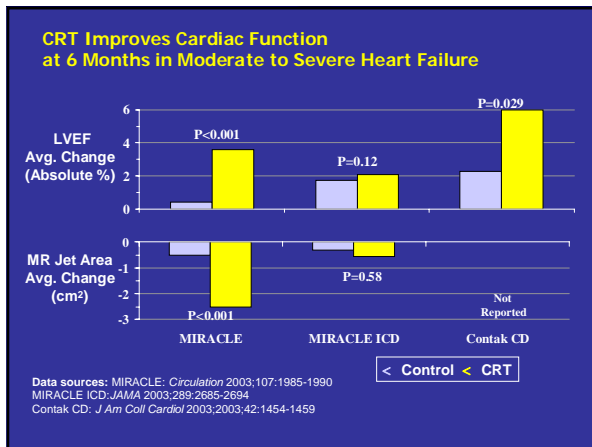
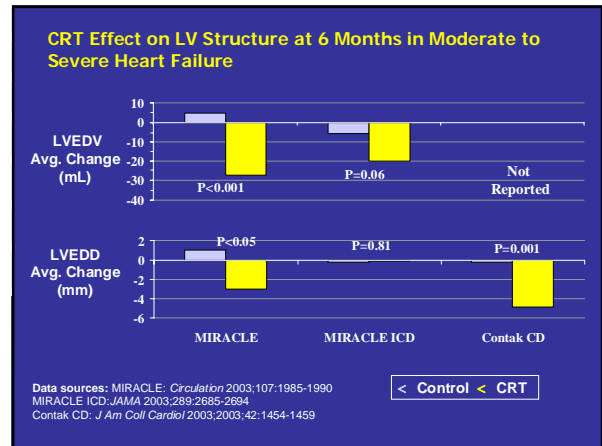
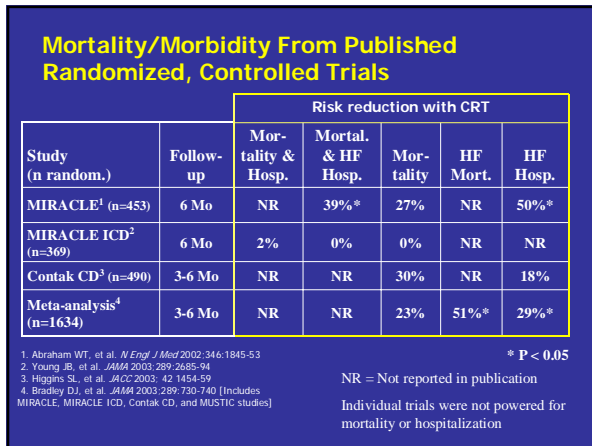
- ### Pharmacologic Management
- #### Angiotensin Receptor Blockers (ARBs)
- Block AT₁ receptors, which bind circulating angiotensin II
 - Examples: valsartan, candesartan, losartan
 - Should not be considered equivalent or superior to ACE inhibitors
 - In clinical practice, ARBs should be used to treat patients who are ACE intolerant due to intractable cough or who develop angioedema

- ### Angiotensin Receptor Blockade
- CHARM and Val-HEFT Trials:
- Addition of candesartan or valsartan to ACE inhibitor and β -blocker in Class II-III heart failure
- 0-10% lower risk of death (P > 0.05)
 - 13-15% lower risk of death or hospitalization for heart failure in both trials, both P < 0.01
 - Higher risk of hypotension, renal insufficiency and hyperkalemia with ARB treatment



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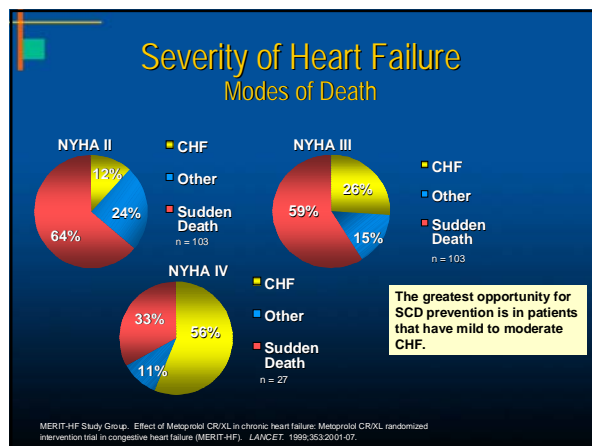


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Achieving Cardiac Resynchronization

Goal: Atrial synchronous biventricular pacing
 Transvenous approach for left ventricular lead via coronary sinus
 Back-up epicardial approach



Conditions Predisposing to Ventricular Arrhythmia in Heart Failure Patients

- Electrophysiological abnormalities
 - Cellular hypertrophy & interstitial fibrosis can result in prolongation of the action potential
 - Increases propensity for early after depolarizations
 - Mechanical stretch can produce electrical activity with slow conduction favoring reentry

Singh S.J Cardiovas Electrophysiol 1997;8:89-97

Conditions Predisposing to Ventricular Arrhythmia in Heart Failure Patients

- Neurohormonal Activation
 - Chronic heart failure triggers maladaptive neurohormonal responses that may predispose to arrhythmia
 - Persistent adrenergic stimulation of the failing heart is maladaptive & arrhythmogenic
 - Adrenergic stimulation enhances automaticity in the His-Purkinje system & areas of scar and ↑ the incidence of VF during ischemia in animal models

Sweeney MO. PACE 2001;24:871-888.

Conditions Predisposing to Ventricular Arrhythmia in Heart Failure Patients

- Electrolyte abnormalities
 - Predisposition to hypokalemia is caused by diuretic therapy, activation of the renin-angiotensin-aldosterone system, and sympathetic activation
 - The effects of hypokalemia on ventricular arrhythmias are amplified in the setting of structural heart disease

Sweeney MO. PACE 2001;24:871-888.

Neurohormonal Interventions: Impact on Survival and Sudden Death

- Use of ace-inhibitors and beta blockers has yielded substantial reductions in mortality due to progressive pump failure and have provided some protection from sudden cardiac death.
- However, mortality from heart failure remains high.
- Several recent studies suggest that perhaps more work is needed to prevent SCD in heart failure.

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Risk of Sudden Death in HF Trials

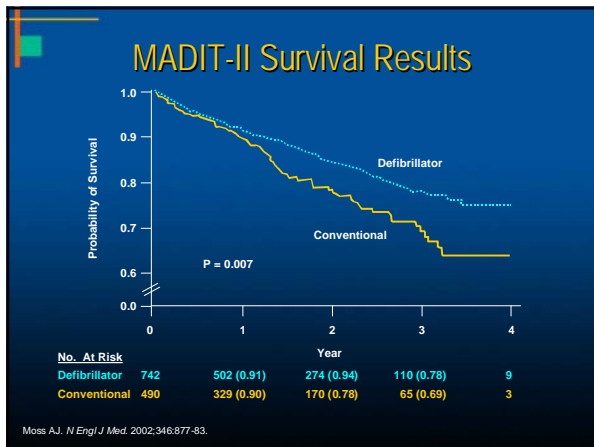
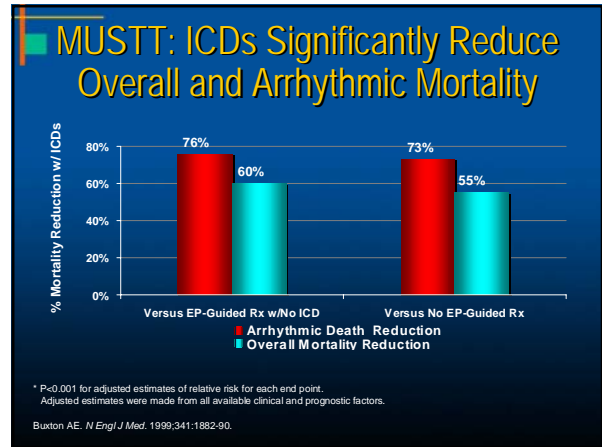
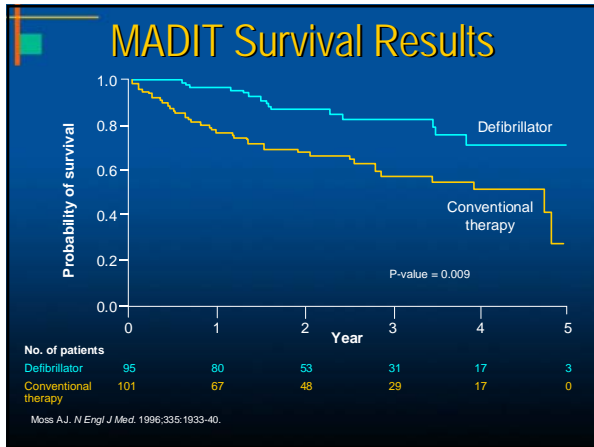
| Study | HF Class | Control (n) | Treatment (n) | Total Mortality Reduction w/Treatment | Sudden Death as a % of Total Death in Control Arm | Sudden Death as a % of Total Death in Treatment Arm |
|---------------------------------------|----------|-------------|---------------|---------------------------------------|---|---|
| MERIT-HF ¹ (Metoprolol) | 2-4 | 2001 | 1990 | 34% | (60%) 132/217 | (54%) 79/145 |
| BEST ² (Bucindolol) | 3,4 | 1354 | 1354 | 10% | (45%) 203/449 | (44%) 182/411 |
| CIBIS-II ³ (Bisoprolol) | 3,4 | 1320 | 1327 | 34% | (36%) 83/228 | (31%) 48/156 |
| CARVEDILOL (U.S.) ⁴ | 2-4 | 398 | 696 | 65% | (48%) 15/31 | (54%) 12/22 |
| RALES ⁵ | 3, 4 | 841 | 882 | 30% | (28%) 110/386 | (29%) 162/478 |

References in slide notes.

SCD in Heart Failure^{1,2}

- Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of pre-mature death in the first 2.5 yrs after diagnosis.
 - ~ 50% of these premature deaths are SCD (VT/VF)
- The role of device therapy?

¹ Baidy G. The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) in: Woosley RL, Singh S. *Arrhythmia Treatment and Therapy*. Copyright 2000 by Marcel Dekker, Inc., pp. 323-342.
² Sweeney MO PACE 2001;24:871-888.



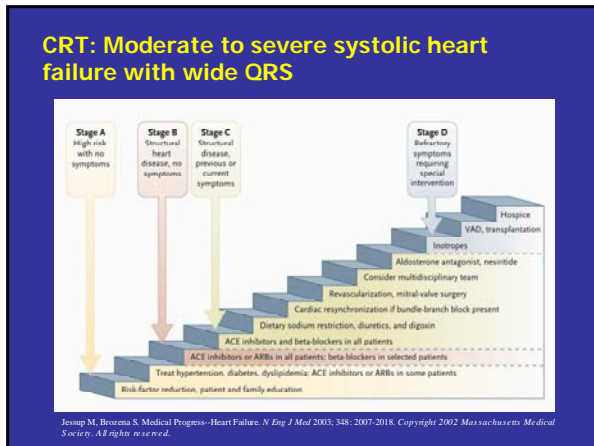
Neurohormonal Interventions in Heart Failure

| Drug Effects on Total and Sudden Cardiac Death Risks ¹ | | | | | | |
|---|---------------------|----------------|----------------|------------------|--------------------------------------|------------------------------|
| | Patients Randomized | LVEF | Drug Tested | ACE-I (% of Pts) | Total Death Risk Reduction (p-value) | SCD Risk Reduction (p-value) |
| TRACE | 2,606 | <36% | Trandolapril | 100% | -22% (≤0.001) | -24% (≤0.03) |
| HOPE | 9,297 | Nominally >40% | Ramipril | 100% | -26% (≤0.005) | -38% (≤0.02) |
| RALES | 1,663 | 25% | Spironolactone | 95% | -30% (≤0.001) | -29% (≤0.02) |
| CIBIS-II | 2,647 | 28% | Bisoprolol | 96% | -34% (≤0.0001) | -44% (≤0.001) |
| MERIT-HF | 3,991 | 28% | Metoprolol | 96% | -34% (≤0.00009) | -41% (≤0.0002) |
| COPERNICUS | 2,289 | 20% | Carvedilol | 97% | -35% (≤0.001) | Not reported |
| SOLVD-T | 2,569 | 25% | Enalapril | 100% | -16% (0.004) | -10% (NS) |
| SOLVD-P | 4,228 | 28% | Enalapril | 100% | -8% (0.3) | -7% (NS) |

¹ Pacifico A, Henry P. *J Cardiovasc Electroanatol*. Vol 14, pp. 764-776, July 2003.

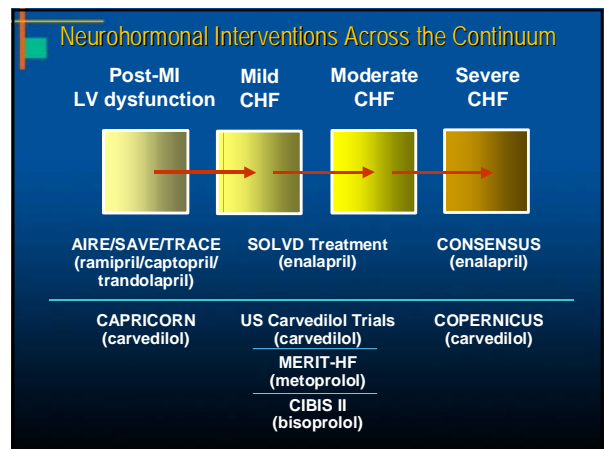
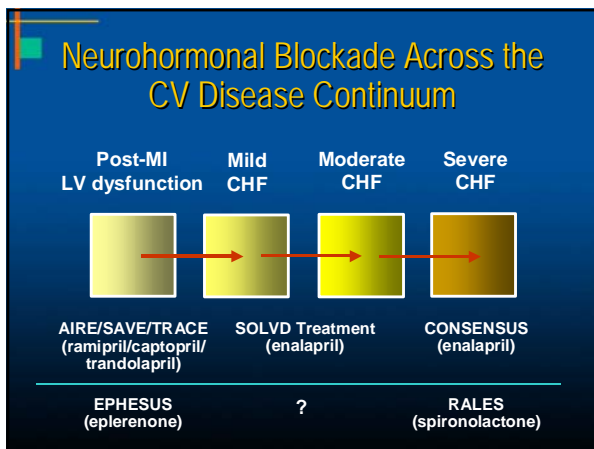
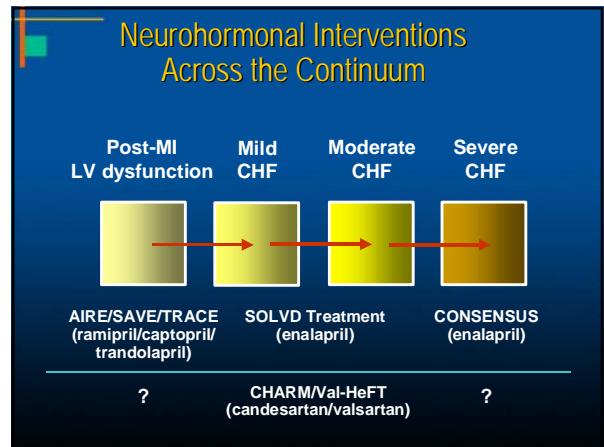
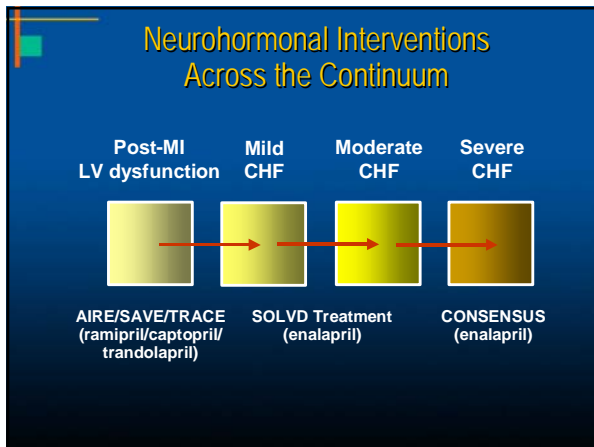
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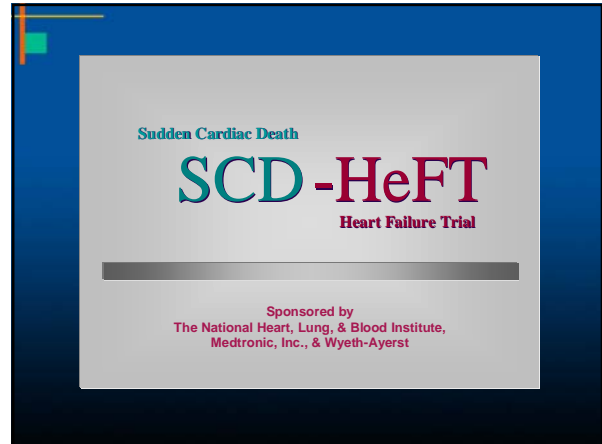
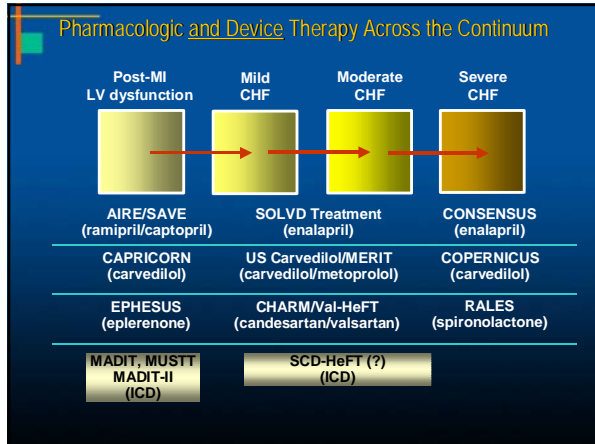
Conclusions

- In patients with LV dysfunction, the combined use of ACE inhibition and beta-blockade is recommended as the cornerstone of therapy.
- Modest incremental benefit may be seen with the addition of other antagonists of the RAS in post-MI LV dysfunction and in chronic heart failure.
- While neurohormonal interventions reduce morbidity and mortality across the cardiovascular disease continuum, post-MI and HF patients with LV dysfunction still have a high rate of sudden cardiac death.
- Therapy with ICDs significantly reduces mortality in post-MI patients with LV dysfunction. These mortality benefits are *on top of optimal pharmacologic therapy*. ICD therapy should be considered standard of care in these patients.
- Data from SCD-HeFT will be critical to understand the role of ICD therapy in ischemic and non-ischemic CHF patients with LV dysfunction.



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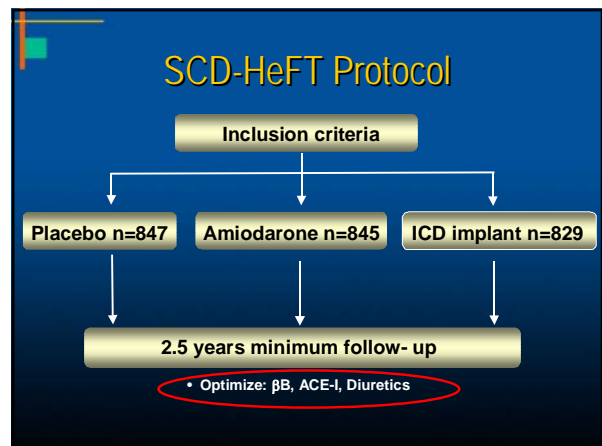
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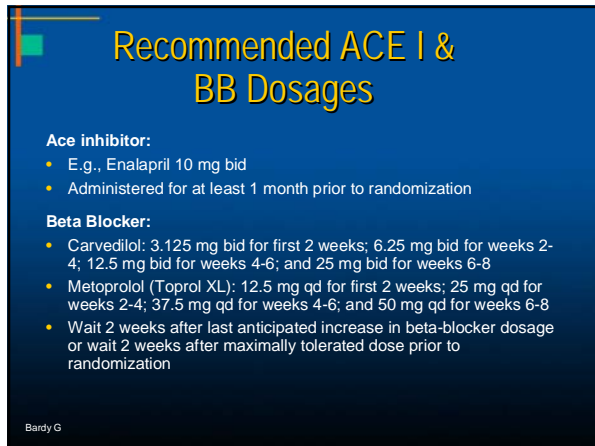
- ### Key Trial Question
- Will Amiodarone and/or an ICD improve survival compared to placebo in patients with NYHA Class II and III CHF and reduced left ventricular ejection fraction ($\leq 35\%$) without a history of sustained VT or VF?

- ### Key Points
- Largest Study – Landmark
 - 2,521 patients, 150 centers, min 2.5 yr f/u
 - Randomized Placebo Controlled Design
 - DCRI – Best in class study management
 - Sponsored by NHLBI, additional funding by Medtronic, Wyeth

- ### SCD-HeFT Endpoints
- **Primary**
 - To compare all cause mortality after 2.5 years of follow-up (Power: 90% to detect 25% benefit)
 - **Secondary**
 - Mortality – Ischemic, Non-Ischemic, Class II, III
 - Cause-Specific Death
 - HF Morbidity & Mortality
 - Consistency of treatment effects across sub groups defined by other variables – age, gender, EF, History of MI, time of MI, QRS width
 - Quality of Life
 - Cost of Care & Cost Effectiveness



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Recommended ACE I & BB Dosages

Ace inhibitor:

- E.g., Enalapril 10 mg bid
- Administered for at least 1 month prior to randomization

Beta Blocker:

- Carvedilol: 3.125 mg bid for first 2 weeks; 6.25 mg bid for weeks 2-4; 12.5 mg bid for weeks 4-6; and 25 mg bid for weeks 6-8
- Metoprolol (Toprol XL): 12.5 mg qd for first 2 weeks; 25 mg qd for weeks 2-4; 37.5 mg qd for weeks 4-6; and 50 mg qd for weeks 6-8
- Wait 2 weeks after last anticipated increase in beta-blocker dosage or wait 2 weeks after maximally tolerated dose prior to randomization

Bardy G