Evidence Based Pharmacotherapy of Chronic Heart Failure

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Presenter Disclosure Information

David Parra, PharmD
Evidence based pharmacotherapy of chronic heart failure
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Objectives

• Review the epidemiology and economics of chronic heart failure
• Understand heart failure staging and NYHA classification
• Discuss recent data on pharmacologic agents used to treat chronic heart failure associated with left ventricular systolic dysfunction
  – Emphasis on dose optimization and monitoring
• Interactively apply the above via case examples

Definitions

“Clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood”...ACC/AHA HF Guidelines 2005
“A clinical syndrome in which cardiac dysfunction (diastolic or systolic) is associated with reduced exercise tolerance, ventricular arrhythmias, and a shortened life span”...Cohn
“A pathophysiologic state in which the heart is unable to pump blood at a rate sufficient to meet the metabolic needs of the body”...Braunwald

Patient Presentation

• Patient symptoms
  – Shortness of breath, cough, orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, edema, fatigue, weight gain
• Physical signs
  – Tachycardia, increasing weight, jugular venous distention or hepatojugular reflux, presence of S3, laterally displaced apical impulse, pulmonary crackles or wheezes, hepatomegaly, peripheral edema

SUPPLY

DEMAND
Epidemiology

• Incidence
  – 550,000 new cases diagnosed yearly
  – 10 cases per 1,000 population after age 65
  – 75% of cases have antecedent hypertension
  – 22% of males and 46% of females are disabled with heart failure within 6 years of myocardial infarction

• Prevalence
  – 5,000,000 people in the United States
  – Upwards of 20-44% have preserved ejection fraction
  – 6 to 10% of people over age of 65 have heart failure


Lifetime Risk of Heart Failure

• At age 40 people free of congestive heart failure (CHF) have a remaining lifetime risk of developing CHF of 21.0 percent for men and 20.3 percent for women
• At age 40, the remaining lifetime risk of CHF in the absence of MI is 11.4 percent for men and 15.4 for women
• At age 80, the remaining lifetime risk is 20.2 percent for men and 19.3 for women


Epidemiology

• Prognosis
  – 286,700 patients die annually as a direct or indirect consequence of heart failure
  – 5-10% annual risk of death in patients with mild symptoms and 30-40% in patients with advanced disease
  – 5 year mortality rate is 50%
  – 80 percent of men and 70 percent of women under age 65 who have CHF will die within 8 years
  – Median survival following onset is 1.7 years for men and 3.2 years for women


Temporal Trends

<table>
<thead>
<tr>
<th>Disease State</th>
<th>1-year mortality (men)</th>
<th>1-year mortality (women)</th>
<th>5-year mortality (men)</th>
<th>5-year mortality (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure*</td>
<td>30%</td>
<td>28%</td>
<td>78%</td>
<td>57%</td>
</tr>
<tr>
<td>1950-1969</td>
<td>41%</td>
<td>28%</td>
<td>75%</td>
<td>59%</td>
</tr>
<tr>
<td>1970-1979</td>
<td>33%</td>
<td>27%</td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td>1990-1999</td>
<td>28%</td>
<td>24%</td>
<td>59%</td>
<td>45%</td>
</tr>
<tr>
<td>All Cancer</td>
<td>38%</td>
<td>37.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td></td>
<td></td>
<td>38.6%</td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td></td>
<td></td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td>14.1%</td>
<td></td>
</tr>
</tbody>
</table>

*All values adjusted for age and reported in patients who survived the initial 30 days after the onset of heart failure (Framingham cohort). Cancer survival rates derived from Surveillance, Epidemiology, and End Results (SEER) program 1973-1998

Economic Burden

(2002 principle discharge diagnosis for heart failure ICD-9 428.0-428.9)

<table>
<thead>
<tr>
<th>Total discharges</th>
<th>Charges, $ (mean)</th>
<th>Aggregate “bill&quot; $</th>
<th>In-hospital deaths</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,027,166</td>
<td>20,369</td>
<td>20,888,372,173</td>
<td>44,737 (4.36%)</td>
<td>46%</td>
</tr>
</tbody>
</table>

http://www.ahrq.gov/Hcupnet.asp accessed April 21, 2005

Economic Burden

• 12 to 15 million office visits each year
• 6.5 million hospital days each year
• Heart failure is the most common Medicare diagnosis-related group (DRG), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis
• Costs accounted for 5.4% of total U.S. health care budget in 1991

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)
### Economic Burden

(estimated direct costs for 2006: 26.8 billion)

- **Drugs/ Medical Durable:** (3.1 billion) 11.5%
- **Physicians/Other Providers:** (2 billion) > 7.5%
- **Home Health:** (2.4 billion) 9%
- **Hospital/Nursing Home:** (19.3 billion) > 73%


### Classification

**NYHA Functional Capacity**

- **Class I:** No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
- **Class II:** Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
- **Class III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
- **Class IV:** Unable to carry on any physical activity without discomfort. Symptoms present at rest. With any physical activity, symptoms increase.


### Stages of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk of developing HF because of presence of conditions associated with development of HF. No structural or functional abnormalities of the heart and not yet shown subclinical HF</td>
<td>HTN, CAD, diabetes mellitus, obesity, metabolic syndrome, history of rheumatic fever, family history of cardiomyopathy, history of cardiotoxic drug therapy or alcohol abuse</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with development of HF, but have never shown subclinical HF</td>
<td>Left ventricular hypertrophy or fibrosis, asymptomatic valvular heart disease, previous MI, left ventricular dilation or hypococontractility (low EF)</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have current or prior symptoms of HF associated with underlying structural heart disease</td>
<td>Known structural heart disease AND shortness of breath and fatigue, reduced exercise tolerance</td>
</tr>
<tr>
<td>D</td>
<td>NYHA IV Patients with advanced structural heart disease marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions</td>
<td>Marked symptoms despite maximal medical therapy, frequent hospitalizations for HF, hospice setting for management of HF, continuous intravenous support</td>
</tr>
</tbody>
</table>


### Goals of Therapy

- **Survival**
- **Morbidity**
- **Exercise capacity**
- **Quality of life**
- **Neurohormonal changes**
- **Progression of CHF**
- **Symptoms**

(AHA / ACC HF guidelines 2001)


### Treatment: Non Pharmacologic

- Maintenance of fluid balance (sodium restriction < 3grams/day, daily weights)
- Tobacco and alcohol cessation
- Management of cardiac comorbidities (obesity, hypertension, hyperlipidemia, diabetes mellitus)
- Aerobic activity (stable NYHA I-III)
- Immunizations
- Coronary revascularization
- Biventricular pacing
- Enhanced external counterpulsation therapy
- Surgical ventricular restoration
- Left ventricular assist devices/Heart transplant
- Compassionate end of life care/hospice
Treatment: Pharmacologic

- Aimed at mechanisms that mediate the progression of heart failure
  - Neurohormonal activation
    - Norepinephrine
    - Aldosterone
    - Endothelin
    - Angiotensin II
    - Vasopressin
    - Cytokines (e.g. tumor necrosis factor)

Renin-Angiotensin-Aldosterone System

Non ACE Pathways
- t-PA
- Cathepsin G
- Chymase
- CAGE
- Chymase
- Cathepsin G
- t-PA
- AT1 Receptor
- AT2 Receptor

ACE Pathways
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- AT1 Receptor
- AT2 Receptors
- Aldosterone Antagonists

- Bradykinin
- Inactive Peptides
- Antihypertrophic, proapoptotic ??

Today’s Pharmacotherapy May Not be Tomorrow’s

"The Foxglove’s leaves, with caution given, Another proof of favouring Heaven, Will happily display; The rapid pulse it can abate; The hectic pulse it can moderate; And blest by Him whose will is fate, May give a lengthened day.”

1818

What’s “Good” Today, Might Not Hold True Tomorrow

"The shock of facing what your figure may become—avoid that future shadow—when tempted, Reach for a Lucky instead—it’s toasted"

Digitalis Glycosides: Digoxin

- Mechanism of action
  - Inhibit Na⁺-K⁺ ATPase pump in cardiac cells → increased contractility
  - Inhibit Na⁺-K⁺ ATPase pump in non-cardiac cells → sensitization of cardiac baroreceptors decreasing sympathetic CNS outflow
  - Inhibit Na⁺-K⁺ ATPase pump in renal cells → reduction in renal tubular absorption of sodium and increased presentation to distal tubules → suppression of renin secretion

- Efficacy in heart failure
  - Short term studies
  - Withdrawal studies
  - One long-term prospective, randomized, study (DIG Trial)

DIG Trial

- To evaluate the effects of digoxin in patients with heart failure and normal sinus rhythm
  - Mortality from any cause (primary endpoint)
  - Mortality from cardiovascular causes (secondary endpoint)
  - Mortality from worsening heart failure (secondary endpoint)
  - Hospitalization for worsening heart failure (secondary endpoint)
  - Hospitalization for other causes (secondary endpoint)

- Multicenter, randomized, double-blind, placebo-controlled trial
- 3,800 patients with NYHA I-IV heart failure followed for 3-5 years
- Stratified according to center and EF < 45 or >45

DIG Trial: Results

- No statistical differences
  - All cause mortality
  - Mortality due to cardiovascular causes
  - Mortality due to worsening heart failure
- Statistical difference in favor of digoxin
  - Hospitalization for worsening heart failure (RR 0.72; p<0.001)
  - Hospitalization for any causes (RR 0.92; p=0.006)


DIG Trial Summary

- Digoxin reduces morbidity (hospitalizations) due to heart failure, but not mortality
  - 13 patients need to be treated to prevent one admission for heart failure over 3 years
  - 36 patients need to be treated to prevent one admission for any reason over 3 years
- Role is still controversial, but it is recommended to improve the clinical status of patients with heart failure due to left-ventricular systolic dysfunction, and should be used in conjunction with diuretics, ACE-I, and a beta-blocker

Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83(2A):1A-38A.

Does Dose Matter?

DIG Trial: Survival Analysis Based on Serum Drug Concentration

- Higher serum drug concentrations were associated with increased mortality rates (p=0.006 for trend)
  - 0.5-0.8ng/mL, 29.9%; 0.9-1.1ng/mL, 38.8%; ≥1.2ng/mL, 48%
- Lower serum drug concentrations (not higher) had lower mortality than placebo group (p<0.05)
  - 0.5-0.8ng/mL, 6.3% lower mortality
  - ≥1.2ng/mL, 11.8% higher mortality
- Another sub-analysis revealed women had higher death rate on digoxin versus placebo, but analysis not adjusted for digoxin levels
- Doses targeted to traditional levels not warranted, and probably harmful; ideal serum drug range 0.5 to 0.8ng/mL


DIG Trial: Analysis of Digoxin Levels

- Higher serum drug concentrations were associated with increased mortality rates (p=0.006 for trend)
  - 0.5-0.8ng/mL, 29.9%; 0.9-1.1ng/mL, 38.8%; ≥1.2ng/mL, 48%
- Lower serum drug concentrations (not higher) had lower mortality than placebo group (p<0.05)
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Digoxin

- Initiation and Maintenance
  - Low doses of 0.125mg to 0.25mg daily
  - Tend to use 0.125mg daily in elderly, renal insufficiency, and if significant renal insufficiency every other day dosing
  - Baseline level reasonable and again if changes in clinical condition, suspicion of toxicity, changes in renal function

Digoxin

• Contraindications
  – 2-3rd degree heart block (without PM)
  – Wolff-Parkinson-White with Afib
  – Ventricular fibrillation
  – Hypersensitivity

• Precautions
  – Amyloid cardiomyopathy
  – Idiopathic hypertrophic subaortic stenosis
  – Constrictive pericarditis
  – Others…

• Adverse Reactions
  – Heart block
  – CNS (dizziness, visual disturbances, confusion, weakness)
  – Dermatologic: rash (1.6%) 
  – Gastrointestinal: nausea, vomiting, diarrhea
  – Others: Increased estrogen levels, impotence

Diuretics (non aldosterone antagonists)

• Mechanism of action
  – Inhibit reabsorption of sodium or chloride at loop of Henle (loop diuretics)
  – Inhibit reabsorption of sodium in distal tubule (thiazides, K+ sparing diuretics)

• Efficacy in heart failure
  – Short term: reduce JVP, pulmonary congestion, peripheral edema, body weight
  – Intermediate term: improve cardiac function, symptoms, and exercise tolerance
  – Long term: no studies completed evaluating morbidity or mortality

• Role in heart failure
  – Rapid symptomatic benefit in hours/days
  – Only drugs in heart failure that can adequately control fluid retention
  – Should not be used alone in treating heart failure
  – Prescribe to all patients with evidence of fluid retention and most with prior history of

Diuretics (non aldosterone antagonists)

• Initiation and Maintenance
  – Loop diuretics are the mainstay of therapy
  – Low doses with titration until urine output increases, and weight decreases (generally by 0.5 to 1.0kg daily)
  – Sodium restriction vital
  – May need to tolerate some degree of hypotension and/or renal insufficiency until fluid retention resolved
  – Once fluid retention resolved maintenance dose should be continued with dose reassessed and adjusted periodically
  – Patients should be educated on self-adjustment based on weight and symptoms
  – May need to use 2 or more diuretics (thiazide + loop) in combination for enhanced effect

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximal Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>12.5-25mg once</td>
<td>100mg</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>25mg once or twice</td>
<td>200mg</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>2.5mg once</td>
<td>5mg</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5mg once</td>
<td>20mg</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5mg once</td>
<td></td>
</tr>
<tr>
<td>Loop</td>
<td>0.5-1mg once or twice</td>
<td>10mg</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>20-40mg once or twice</td>
<td>600mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>18-20mg once</td>
<td>200mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium-sparing</td>
<td>5mg once</td>
<td>20mg</td>
</tr>
<tr>
<td>Amiloride</td>
<td>50-75mg twice</td>
<td>200mg</td>
</tr>
<tr>
<td>Triamterene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diuretics (non aldosterone antagonists)

- Contraindications
  - Hypersensitivity
- Precautions/Adverse events
  - Renal impairment
  - Hypotension
  - Electrolyte disturbances
  - Rash

Angiotensin Converting Enzyme Inhibitors (ACE-I)

- Mechanism of action
  - Inhibits conversion angiotensin I to angiotensin II
    - With chronic use there is partial “escape” from inhibition with “normalization” of angiotensin levels (alternative pathways)
  - Block degradation of bradykinin
- Efficacy in heart failure
  - Cornerstone of drug therapy for heart failure associated with left ventricular systolic dysfunction (based on numerous studies)
  - Reduced morbidity (all patients) and mortality (in symptomatic patients) in patients with left ventricular systolic dysfunction during trial periods
  - Long-term 12 year follow-up also revealed mortality benefit in asymptomatic patients (X-SOLVD, Lancet 2003)

Angiotensin Converting Enzyme Inhibitors (ACE-I)

- Populations studied
  - Systolic dysfunction (EF ≤ 35-40%) treated with diuretics with or without digoxin
  - Wide range of patients, elderly, women, causes of LV dysfunction and severity of LV dysfunction
  - Excluded preserved systolic function, systolic blood pressure < 90mmHg, moderate renal insufficiency (serum creatinine > 2.5mg/dL), bilateral renal artery stenosis, hyperkalemia

Mortality Reduction with ACE-i

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE-I</th>
<th>Clinical Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>SOLVD treatment</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril</td>
<td>CHF</td>
</tr>
<tr>
<td>Vheft-II</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril</td>
<td>CHF / LVD</td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>LVD</td>
</tr>
<tr>
<td>SMILE</td>
<td>Zofenopril</td>
<td>High risk</td>
</tr>
<tr>
<td>HOPE</td>
<td>Ramipril</td>
<td>High risk</td>
</tr>
</tbody>
</table>
### Angiotensin Converting Enzyme Inhibitors (ACE-I)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Dose (CHF)*</th>
<th>Maximal Daily Dose (HTN)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril (Lotensin®)</td>
<td>Not FDA approved 80mg</td>
<td></td>
</tr>
<tr>
<td>Captopril (Capoten®)</td>
<td>50mg three times daily 450mg</td>
<td></td>
</tr>
<tr>
<td>Enalapril (Vasotec®)</td>
<td>10-20mg twice daily 40mg</td>
<td></td>
</tr>
<tr>
<td>Fosinopril (Monopril®)</td>
<td>40mg daily 80mg</td>
<td></td>
</tr>
<tr>
<td>Lisinopril (Zestril®, Prinivil®)</td>
<td>20-40mg daily 80mg</td>
<td></td>
</tr>
<tr>
<td>Moexipril (Univasc®)</td>
<td>Not FDA approved 30mg</td>
<td></td>
</tr>
<tr>
<td>Perindopril (Aceon®)</td>
<td>40mg twice daily 80mg</td>
<td></td>
</tr>
<tr>
<td>Quinapril (Accupril®)</td>
<td>40mg twice daily 80mg</td>
<td></td>
</tr>
<tr>
<td>Ramipril (Altace®)</td>
<td>10mg once daily 20mg</td>
<td></td>
</tr>
<tr>
<td>Trandolapril (Mavik®)</td>
<td>4mg daily 8mg</td>
<td></td>
</tr>
</tbody>
</table>


### Contraindications
- Bilateral renal artery stenosis
- Unilateral stenosis of single functional kidney
- Angioedema
- Pregnancy (2nd, 3rd trimester)
- $K^+ > 5.5$ mmol/L that cannot be reduced

### Precautions
- Renal impairment (Creatinine ≥ 3mg/dL)
- Systolic blood pressure < 80mmHg

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### Does Dose Optimization Matter?

The Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial

To compare the efficacy and safety of low and high doses of ACE inhibition on the risk of death and hospitalization


### ATLAS

**Trial Design**

- Multicenter, randomized, double-blind, parallel group trial
- 3164 patients with NYHA II, III or IV heart failure
- 18 month recruitment period, with minimum follow-up of 3 years
- Treatment duration: 3.0 to 4.5 years
- Randomized to 2.5-5mg versus 32.5-35mg lisinopril

ATLAS

Major outcome findings

‘High dose’ lisinopril versus ‘low dose’ lisinopril resulted in risk reductions of:

- **Primary endpoint**
  - 8% in all-cause mortality (non-significant trend: p=0.128)

- **Secondary endpoints**
  - 12% in combined all-cause mortality and all-cause hospitalization (p=0.002)
  - 10% in cardiovascular mortality (non-significant trend: p=0.073)
  - 8% in combined all-cause mortality and cardiovascular hospitalization (p=0.036)
  - 9% in combined cardiovascular mortality and hospitalization (p=0.027)
  - 8% in fatal and non-fatal MI and hospitalization for unstable angina (p=0.074)

- **Post-hoc analysis**
  - 15% in combined all-cause mortality and hospitalization for heart failure (p=0.001)


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ATLAS compared with SOLVD

<table>
<thead>
<tr>
<th>Treatments compared</th>
<th>Reduction in risk of death</th>
<th>Reduction in risk of death or hospitalization for HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose vs. placebo (SOLVD)</td>
<td>16%</td>
<td>26%</td>
</tr>
<tr>
<td>Low dose vs. placebo (not studied)</td>
<td>not known</td>
<td>not known</td>
</tr>
<tr>
<td>High dose vs. low dose (ATLAS)</td>
<td>8%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Use of low dose ACE-I provides only about half of the benefit that can be achieved with high dose.


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ATLAS

Dose Optimization Does Matter!

- **Increased direct costs**
  - Drug costs
  - Additional provider visits for titration of dose

- **No overall increase in adverse events**

- **Reduced hospital bed occupancy**
  - 24% reduction in admission for heart failure over 3 years (1576 versus 1199)
  - 13% reduction in admission for any reason over 3 years (4397 versus 3819)

- **Potential savings**

  Hospital costs in US could be reduced by $2 billion/year


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Beta-blockers

- **Mechanism of Action**
  - Cardiac myocyte protection of receptors from catecholamines
  - Prevention of binding of auto-antibodies to adrenoceptors
  - Heart rate reduction
    - Improved (diastolic) coronary artery flow and myocardial oxygenation
    - Improved force-frequency relationship
  - Cardiac myocyte energy conservation

Beta-blockers

- **Efficacy in heart failure**
  - Along with ACE-I cornerstone of drug therapy for heart failure associated with left ventricular systolic dysfunction (based on several large RCT studies)
  - Reduced morbidity and mortality in symptomatic patients with left ventricular systolic dysfunction during trial periods

Characteristics of Beta-blockers

- **Selectivity**
  - Cardiodeselective: β₁
  - Not Cardiodeselective: β₂, β₃
  - Ancillary receptor blockade: α₁
- **Intrinsic Sympathomimetic Activity (ISA)**
  - Not desirable in ischemic patients
- **Membrane Stabilizing Activity (MSA)**
  - Stabilize action on action potential
  - Important experimentally, but not relevant to clinical management of arrhythmias
- **Lipid Solubility**
  - May play a role in side effects and tolerability

Beta-blockers

Cleland, J. http://www.cardio.net

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Beta-blockers

- **Populations Studied**
  - Symptomatic systolic dysfunction (EF ≤ 35-45%) treated with ACE-I, diuretics with or without digoxin
  - Wide range of patients, elderly, women, causes of LV dysfunction and severity of LV dysfunction
  - Excluded preserved systolic function, systolic blood pressure < 85mmHg, heart rate < 65 beats per minute


- **Initiation and Maintenance**
  - Very low doses with titration (every 2 weeks in trials) after demonstrated tolerability of dose
  - Titrated as tolerated to doses demonstrated to provide a clinical benefit
  - Studies evaluating beta-blockers titrated to a target or maximally tolerated dose NOT therapeutic response
  - Concurrent diuretic therapy may need to be adjusted initially or after therapy started
  - 85% of patients can tolerate short- and long-term therapy
  - Clinical responses may not become apparent for 2-3 months


- **Beta-blockers: Management of Adverse Events**
  - Fluid retention and worsening heart failure- more likely to occur during initiation and first several months
    - Daily weights and careful adjustment of diuretics
  - Hypotension- more likely with carvedilol (administer with food)
    - Administer ACE-I separately or temporarily reduce ACE-I
  - Bradycardia and heart block- risk of 5-10% as dose increased
    - If symptomatic or > 1st degree block need to reduce dose
  - Fatigue/Weakness- may resolve with time or reduction in dose

- **Beta-blockers**
  - **Contraindications**
    - Second or third heart block
    - Sinus bradycardia
    - Sick sinus syndrome
  - **Precautions**
    - Asthma
    - Severe peripheral arterial disease
    - Uncompensated cardiac failure


- **Other Adverse Reactions**
  - Cold peripheries
  - Bronchoconstriction
  - Interference with autonomic and metabolic responses to hypoglycemia

Does Dose Optimization Matter?

### Clinical Trial Data (RCT)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean Dose</th>
<th>Demographics</th>
<th>Primary Endpoint Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol</td>
<td>45 + 2.5mg daily; 80% on 50mg daily</td>
<td>1094 patients, 76% male, Ischemic 48%, Non-ischemic 52% NYHA II (54%), III (41%), IV (5%); EF 23% ACE (95%), Loop (95%) Digoxin (91%)</td>
<td>38% reduction in death or hospitalization due to CV reasons (13.8% (c) vs. 24.6% (p), p &lt; 0.001)</td>
</tr>
<tr>
<td>Merit-HF Metoprolol Succinate</td>
<td>159mg (100mg tartrate equivalent) daily, 85% on 100mg daily; 64% on 200mg daily; 13.9% dc'd drug, 15.3% dc'd placebo</td>
<td>3991 patients, 77% male, Ischemic 65%, Non-ischemic 35% NYHA II (41%), III (56%), IV (3.4%); EF 26% ACE/All (95%), Diuretic (91%) Digoxin (67%)</td>
<td>34% reduction in all cause mortality, p=0.00009; 145 deaths (7.2%) in metoprolol group vs. 217 deaths (11.0%) in placebo group 19% reduction in total mortality or all-cause hospitalization, p&lt;0.01; 641 events (32%) in metoprolol group vs. 767 events (38%) in placebo group</td>
</tr>
</tbody>
</table>

### COMET Carvedilol versus Metoprolol Tartrate

- Target dose 50mg carvedilol and 100mg metoprolol tartrate
- Average dose 41.5mg carvedilol and 85mg metoprolol tartrate
- 32% of patients in each group discontinued therapy

- 3829 patients, 79% male, Ischemic 51%, Non-ischemic 49% NYHA II (48%), III (43%), IV (4%); EF 26%
- ACE/All (98%), Diuretic (99%) Digoxin (66%)
- 37% reduction in all cause mortality, p<0.0017; 512 deaths (34%) in carvedilol group vs. 600 deaths (40%) in metoprolol tartrate group
- No significant difference in endpoint of mortality or all-cause admission

### Newer and Resurrected Therapies

- Angiotensin II Receptor Antagonists (ARBs)
- Aldosterone Antagonists
- Hydralazine/Isosorbide Dinitrate

### Renin-Angiotensin-Aldosterone System

- Non ACE Pathways
  - Angiotensinogen
  - Chymase
  - CAGE
- ACE Pathways
  - Angiotensin I
  - Angiotensin II
  - Renin
  - Bradykinin
  - ACE
  - Inactive Peptides
- All-Receptor Blockers
  - AT1 Receptor
  - AT2 Receptors
  - Antihypertrophic, proapoptotic ???
- Vasodilatation
- Cell Growth Inhibition
- Thrombosis
- Sodium & Fluid Retention
- Aldosterone Release
- Sympathetic Activation

### All Receptor Blockers

- Pursued based on rationale that
  - All production occurs despite ACE inhibition
  - Interference of RAS without inhibition of kinase would produce benefits of ACE-Is while minimizing risk of adverse reactions
All Receptor Blockers

• Efficacy in heart failure in ACE-I intolerant patients
  – Indicated in ACE-I intolerant patients (i.e. cough) to reduce morbidity and mortality in symptomatic patients (CHARM-Alternative)

• Efficacy in heart failure versus an ACE-I
  – ELITE II (heart failure) showed a trend towards worse outcome with losartan versus captopril
  – OPTIMAAL (post MI heart failure) also showed a trend towards worse outcome with losartan versus captopril
  – VALIANT (post MI heart failure) showed valsartan was as effective as captopril

All Receptor Blockers

• Efficacy in heart failure with an ACE-I
  – ValHeFT (heart failure) showed reduction in morbidity (not mortality) when added to ACE-I unless patient was also on beta-blocker (trend towards increase in mortality)
  – CHARM-Added (heart failure) showed reduction in combined CV morbidity and mortality with combination
  – VALIANT (post MI heart failure) did not show added benefit with the combination
Did dosing of the agents contribute to these findings?

Dosing of ARBs in LV Dysfunction Trials

- **ARB versus ACE-I**
  - ELITE II (heart failure): Losartan 50mg vs. captopril 50mg tid
  - OPTIMAAL (post MI heart failure): Losartan 50mg (45mg avg.) vs. captopril 50mg tid (132mg avg. daily dose)
  - VALIANT (post MI heart failure): Valsartan 160mg bid (247mg avg. daily dose) vs. captopril 50mg tid (117mg avg. daily dose)
  - Low dose ARB (losartan 50mg) no benefit over high dose ACE-I
  - High dose ARB (valsartan 160mg bid) equal to high dose ACE-I

Aldosterone Antagonists
Aldosterone Antagonists

- Mechanism of action
  - Block aldosterone binding at mineralcorticoid receptors in kidney, heart, blood vessels, and brain
  - Blockade of aldosterone in distal renal tubule \(\rightarrow\) increased \(\text{Na}^+\text{Cl}^-\) and water excretion and potassium retention
- Efficacy in heart failure
  - Spironolactone reduced total mortality 30% over 2 years in NYHA late III and IV patients


Aldosterone Antagonists

- Eplerenone shown to reduce total mortality 15% (\(p=0.008\)) over 16 months in post MI patients with EF <35% and symptoms of heart failure (if diabetic, symptoms were not required for enrollment)
- Eplerenone reduced death from cardiovascular causes or hospitalization for cardiovascular events by 13% (\(p=0.002\))
- Eplerenone reduced sudden cardiac death by 21% (\(p=0.03\))


Aldosterone Antagonists

- Exclusions from heart failure studies
  - Serum creatinine > 2.5mg/dL
  - Serum potassium > 5.0 mEq/L
- Dosing
  - Spironolactone: 12.5mg-25mg daily titrated to 50mg in 8 weeks if symptomatic or reduced to every other day if hyperkalemic
  - Eplerenone: 25mg daily titrated to 50mg in 4 weeks if \(K^+ < 5.0\) mEq/L
- Creatinine and potassium monitoring
  - 3 days, 1 week post initiation, and one week post dose changes, and monthly for 1st 3 months then probably at least every 3-4 months thereafter


Aldosterone Antagonists

- Adverse Reactions
  - Serious hyperkalemia (>6.0 mmol/L): 5%
  - Renal insufficiency
  - Gynecomastia/breast pain (10% spironolactone)
  - Rash
  - Other

- Listed contraindications (eplerenone)
  - Serum potassium >5.5 mEq/L at initiation
  - Creatinine clearance <30 mL/min
  - Concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir

Isosorbide Dinitrate + Hydralazine

NITRATES HEMODYNAMIC EFFECTS

1- VENOUS VASODILATATION
   - Pulmonary congestion
   - Ventricular size
   - MVO₂

2- Coronary vasodilatation
   - Myocardial perfusion

3- Arterial vasodilatation
   - Afterload

4- Others
   - Cardiac output
   - Blood pressure

VHeFT-1
N Engl J Med 1986;314:1547

23% reduction in mortality at 3 years

Nitrates + Hydralazine

Probability of Death

VHeFT II

Baseline Medications for heart failure (% of patients)
- Diuretic ~90%; ACE inhibitor or ARB ~85%, Beta-blocker ~75%, Digoxin ~60%, Spironolactone ~40%
Calcium Channel Antagonists

- **Summary**
  - No role in treating chronic heart failure associated with LV systolic dysfunction
  - Newer agents (felodipine ER, amlodipine) may be used safely for other indications (i.e. angina, hypertension) in patients with chronic heart failure

Anticoagulation

- **Summary**
  - Most justified in patients with heart failure who have had a previous embolic event or are in atrial fibrillation

Anti-arrhythmics

- Patients with heart failure may have frequent and complex ventricular arrhythmias and a high risk of sudden death
- Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias
- The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF
- It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias

Putting it All Together: Clinical Applications

- Asymptomatic LV systolic dysfunction
  - Ace-Inhibitor
  - Beta-Blocker
- Heart failure with LV systolic dysfunction
  - ACE-Inhibitor (mortality benefit); if ACEi intolerant AII blocker
  - Beta-Blocker (mortality benefit)
  - Digoxin (< 0.9ng/mL) if still symptomatic (morbidity)
  - Diuretics added at anytime if fluid overloaded
  - Aldosterone Antagonist if NYHA III-IV or post MI with failure (mortality benefit when added to other agents)
  - Nitrate/Hydralazine if black (mortality benefit)
  - AII blocker can be considered (morbidity benefit, but no mortality benefit, when added to other agents)

Pharmacologic Management of Diastolic Heart Failure

- Lack of controlled clinical trials
- Focus on control of physiological factors
  - Blood pressure
  - Heart rate
  - Blood volume
  - Myocardial ischemia
- Angiotensin II Receptor blockers
  - Reduce hospitalization in symptomatic heart failure patients with preserved ejection fraction (EF > 40%); CHARM-Preserved

ACC / AHA 2005 Drug Recommendations for Patients With HF and Normal LVEF

- **Class I**
  - Diuretics to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF (LOE: C)
- **Class IIb**
  - Use of beta-adrenergic blocking agents, ACE inhibitors, AII receptor blocker, or calcium antagonists in patients with HF and normal LVEF and controlled HTN might be effective to minimize symptoms of HF (LOE: C)
  - The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established (LOE: C)
Case Presentation 1

A 60 year old male with non ischemic cardiomyopathy (EF 20%) presents to clinic (1999) for medication management. S/P recent hospitalization for heart failure, and cardiac catheterization that revealed no significant CAD.

Other PMH: h/o PUD, chronic LBP, HTN, history of NSVT

Symptoms: DOE with 2-4 blocks walking, 1+ BLE stable, no PND, “very fatigued with little activity”—NYHA Class III

Diet: Low salt (<2gm sodium day), “cautious” with fluids

Vitals: BP 130/80mmHg, pulse 82, Weight 194 lbs

Labs: wnl (Cr 1.2mg/dL (0.5-1.3), K+ 4.5meq/L (4.0-5.2), LDL 110mg/dL.

Meds: ASA EC 81mg daily, Lisinopril 5mg daily, Furosemide 40mg daily

Q: What would be reasonable modifications in order to maximize the pharmacologic treatment of this patient’s heart failure?

Case Presentation 1

1) Increase lisinopril?
2) Initiate beta-blocker?
3) Initiate digoxin?

Case Presentation 1

• Increase lisinopril?
  – Based on ATLAS study this would reduce morbidity
• Initiate beta-blocker?
  – Based on MERIT-HF, Carvedilol studies, and others beta, blockers reduce morbidity and mortality in NYHA II-III patients
• Initiate digoxin?
  – Based on DIG Trial this would reduce morbidity

Case Presentation 1

Lisinopril was increased over several weeks to a dose of 40mg daily. Patient returns for follow-up visit with continued complaints of DOE with 6 blocks, fatigue, and bilateral edema (1+). No PND, dizziness or lightheadedness, or orthopnea. Fatigue improved per patient.

Vitals: BP 115/70, pulse 84, Weight 195 lbs

Labs: wnl (Cr 1.4 up from 1.2), K+ 5.4 up from 4.5

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily

Q: What changes should be considered (if any) at this time?

Case Presentation 1

• Decrease lisinopril? (serum creatinine now 1.4 and potassium 5.4)
• Increase furosemide? (patient still SOB with 1+ BLE)
• Initiate beta-blocker? (patient maximized on ACE inhibitor and still symptomatic)
• Initiate digoxin?

Case Presentation 1

• Decrease lisinopril?
  – The slight changes in serum creatinine and potassium manifested by patient do not warrant this
• Increase furosemide?
  – Symptoms are still stable (weight, 1+ edema, SOB) and lungs CTA
• Initiate beta-blocker?
  – Patient maximized on ACE inhibitor and still symptomatic
• Initiate digoxin?
  – May improve symptoms and reduce morbidity
Case Presentation 1

Patient was initiated on carvedilol 3.125mg twice daily and digoxin 0.125mg daily. He returns in 2 weeks with complaints of increased SOB, increased edema, and weight gain. He also complains of dizziness soon after taking his lisinopril and carvedilol.

Vitals: BP 105/60, pulse 78, Weight 199 (baseline 194), Lungs-rales Labs: wnl, Cr 1.2, K+ 5.2, digoxin trough 0.8ng/mL.

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily, Carvedilol 3.125mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?

- Stop carvedilol? (patient not tolerating, BP too low at 105/60 and patient dizzy and lightheaded)
- Increase carvedilol? (higher doses show more benefit)
- Change beta-blockers?
- Increase digoxin? (level only 0.8ng/mL and patient still symptomatic)
- Decrease lisinopril? (BP too low at 105/60 and patient dizzy and lightheaded)
- Increase furosemide? (rales, increased weight & edema)
- Review timing of carvedilol and lisinopril doses

Case Presentation 1

Furosemide was increased to 80mg daily x 3 days, and then return to 40mg qd with 20mg prn weight/edema. Patient instructed to take carvedilol with food and lisinopril 2 hours later. On return in 1 week patient reports breathing is better, no edema, but still SOB with 6 blocks of walking. No dizziness as long as he takes carvedilol with food and lisinopril 2 hours later. He reports he had to take the 80mg of furosemide daily in order to control weight/edema and SOB.

Vitals: BP 100/65, pulse 78, Weight 195 (baseline 194), Lungs-CTA Labs: wnl, Cr 1.4, K+ 5.0

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 80mg daily, Carvedilol 3.125mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?

- Stop carvedilol? (BP too low at 100/65)
- Increase carvedilol? (higher doses show more benefit)
- Decrease lisinopril? (BP too low at 105/60)
- Nothing?

Case Presentation 1

As patient had only been “stable” again x 1 week nothing was done. He returned in 2 more weeks and over a period of 2 more months his carvedilol was slowly increased.

Patient presents today feeling “good”. Can walk up to 8 blocks without becoming SOB. Minimal edema. Not as fatigued. However, gets dizzy at times, particularly with quick movements.

Vitals: BP 94/60, pulse 58, Weight 193 (baseline 194), Lungs-CTA Labs: wnl, Cr 1.6, K+ 4.8, Magnesium 2.0

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 80mg daily, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?

- Reduce carvedilol? (BP too low at 94/60 and pulse 58)
- Increase carvedilol? (higher doses show more benefit)
- Decrease lisinopril? (BP too low at 94/60)
- Decrease furosemide? (BP too low at 94/60 and pt shows signs of over diuresis-creatinine, weight, symptoms)
- Other diagnostic tests? (i.e. EKG, Holter, EPS study)
Case Presentation 1

Diagnostic tests (EKG/Holter) revealed no rhythm disturbances. Furosemide was decreased to 40mg daily with an extra 20mg as needed. Patient returns in 2 weeks with dizziness resolved. No complaints. Can walk up to 8 blocks without becoming SOB. Minimal edema.

Vitals: BP 102/64, pulse 56, Weight 195 (baseline 194), Lungs-CTA
Labs: wnl, Cr 1.3, K+ 4.9

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily with 20mg as needed, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?

Nothing was done as it was felt that patient was maximized on carvedilol, and doing well with current vitals, and other medications. Patient returned for 12 month follow-up feeling “great”. Can walk “around the mall” without becoming SOB. Minimal if any edema. Fatigued only when he “over-exerts” himself.

Vitals: BP 105/66, pulse 58, Weight 194 (baseline 194), Lungs-CTA
Labs: wnl, Cr 1.3, K+ 4.5

MUGA: EF 28% up from 20%
NYHA Class I-II

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily with 20mg as needed, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily

Case Presentation 1 - Conclusions

- Close monitoring required to optimally treat patients
- Patient education and understanding of therapies essential
- Select therapies based on clinical evidence as well as patient presentation/progress
- Medications can improve, but not “cure” heart failure
- Options are continually changing. Patient may have been a candidate for
  - Aldosterone Antagonist (RALES study, 1999)
  - AII blocker (CHARM study, 2003)
  - AICD? (DEFINITE study, 2003)

Case Presentation 2

Pt is a 66yowm who presents with his wife today (March 1999).

Symptoms: DOE with 2-4 blocks walking, 1+ BLE stable, no PND, “very fatigued with little activity”—NYHA Class III

PMH: CAD, CABG 5v ’83, CHF (EF 20%), Atrial Fibrillation, S/P Vasovagal syncopal episode 4/98, S/P Bronchitis/pneumonia with bronchospasm 1/98, s/p back surgery complicated by meningitis/coma/seizure and a CVA (with residual right hemiplegia), DVT and PE. DM Type II, HTN, hyperlipidemia, DJD, neuropathy LE and UE.

(-)TOB (quit ’83), (-)ETOH (quit ’92 previously heavy drinker)

BP 180/100 standing, 142/82 supine. Pulse 76 supine, 96 standing
Weight # 232 pounds

Labs: Creatinine 1.4, BUN 24, Potassium 4.6
Allergies/Adverse Reactions: NKDA

Medications:
Hyzaar 50/12.5mg bid (losartan/hydrochlorothiazide)
Coumadin
Simvastatin 40mg daily
Insulin

Plan: Change Hyzaar to fosinopril 20mg twice daily, and hydrochlorothiazide 25mg po qd
Case Presentation 2

Visit # 2: Pt denies any DOE, but is limited by severe peripheral neuropathy rather than his exercise capacity. He has had occasional dizziness, which he attributes to an inner ear problem. Has had no edema, angina, PND since last visit one month ago. 
BP 160/90 pulse 80; Weight # 231

Medications:
Fosinopril 20mg po bid
Hydrochlorothiazide 25mg po qd
Simvastatin 40mg po qd
Insulin 70/30 42 units qam and 20 units qpm
Gabapentin 300mg po bid
Magnesium Oxide 420mg po qd

Case Presentation 2


P: Metoprolol succinate 25mg po qd
Pt cautioned on worsening sx's heart failure (i.e. edema/weight gain) and to call if they occur (> 2lbs in one day). 
Reviewed daily weights and low salt eating (pt initially refused to consider a low salt diet but agreed upon after discussion).
RTC 2 weeks with PT, Chem 7

Case Presentation 2

Returns in 1 month for 2nd visit:
Pt states he has some LLE edema and edema in one hand since starting metoprolol, but tolerating well. No PND, CP, now with some slight DOE
BP 164/82 pulse 70; Weight # 237 (previous # 231)

Medications:
Metoprolol succinate 25mg po qd
Fosinopril 20mg po bid
Hydrochlorothiazide 25mg po qd
Coumadin 5mg po qd
Simvastatin 40mg po qd
Insulin 70/30 42 units qam and 20 units qpm
Gabapentin 300mg po bid
Magnesium Oxide 420mg po qd
B-Complex qd
Antioxidant vitamin qd

PLAN:
Increase metoprolol succinate 50mg qd and change hydrochlorothiazide to furosemide 20mg qd

Case Presentation 2

• Visit # 4 (2 weeks after visit # 3): Weight up another 2 pounds, edema persisting and furosemide increased to 40mg daily
• Visit # 5 (1 month later): Weight same as visit # 4, BP uncontrolled (still) edema improved, but still some DOE.

Medications:
Metoprolol Succinate 50mg po qd
Fosinopril 20mg po bid
Furosemide 40mg po qd
Coumadin 5mg po qd
Simvastatin 40mg po qd
Insulin 70/30
Glyburide 10mg po bid
Gabapentin 300mg po bid
Magnesium Oxide 420mg po qd
B-Complex qd
Antioxidant vitamin qd

PLAN:
Increase metoprolol succinate to 100mg qd
Add digoxin 0.125mg qd

Case Presentation 2

• Visit # 6 (2 months later): He had stopped digoxin on his own (diarrhea which did not resolve). Digoxin restarted at this visit.
• Several phone contacts over next month as pt felt like “bubble in head”. He stopped digoxin, the restarted and reduced his metoprolol dose and felt better. However, blood pressure uncontrolled and felodipine 2.5mg daily added and patient agreed to try digoxin again and slowly increase metoprolol.

Hyzaar 50/12.5mg bid
(losartan/hydrochlorothiazide)
Coumadin
Simvastatin 40mg daily
Insulin

6 month visit
Digoxin 0.125mg po qd
Metoprolol succinate 100mg po qd
NTG SL prn
Fosinopril 20mg po bid
Furosemide 40mg po qd
Coumadin
Felodipine 2.5mg po qd
Simvastatin 40mg po qd
Insulin 70/30
Glyburide 10mg po bid
Gabapentin 300mg po bid
Magnesium Oxide 420mg po qd
B-Complex qd
Antioxidant vitamin qd
Tylenol prn pain
Case Presentation 2

<table>
<thead>
<tr>
<th>6 month visit</th>
<th>12 month visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin 0.125mg po qd</td>
<td>Digoxin 0.125mg po qd</td>
</tr>
<tr>
<td>Metoprolol succinate 100mg po qd</td>
<td>Metoprolol succinate 200mg po qd</td>
</tr>
<tr>
<td>NTG SL prn</td>
<td>NTG SL prn</td>
</tr>
<tr>
<td>Fosinopril 20mg po bid</td>
<td>Fosinopril 20mg po bid</td>
</tr>
<tr>
<td>Furosemide 40mg po qd</td>
<td>Furosemide 40mg po qd</td>
</tr>
<tr>
<td>Coumadin</td>
<td>Coumadin</td>
</tr>
<tr>
<td>Fedolipine 2.5mg po qd</td>
<td>Fedolipine 2.5mg po qd</td>
</tr>
<tr>
<td>Simvastatin 40mg po qd</td>
<td>Simvastatin 80mg po qd</td>
</tr>
<tr>
<td>Insulin 70/30</td>
<td>Insulin 70/30</td>
</tr>
<tr>
<td>Glyburide 10mg po bid</td>
<td>Insulin Regular prn sliding scale</td>
</tr>
<tr>
<td>Lisinopril 300mg po tid</td>
<td>Glycylcine 10mg po bid</td>
</tr>
<tr>
<td>Magnesium Oxide 420mg po qd</td>
<td>Levetiracetam 0.15mg po qd</td>
</tr>
<tr>
<td>B-Complex qd</td>
<td>Galapentin 300mg po tid</td>
</tr>
<tr>
<td>Antioxidant vitamin qd</td>
<td>B-Complex qd</td>
</tr>
<tr>
<td>Tylenol prn pain</td>
<td>Antioxidant vitamin qd</td>
</tr>
</tbody>
</table>

Case Presentation 2

- Patient continued to feel well over the next several years with no heart failure exacerbations or hospital admissions except a brief stay for chest pain. Spironolactone was added at about his 15 month visit, and other medication adjustments for blood pressure and cholesterol control. He also had fosinopril replaced with irbesartan as pulmonologist thought it was exacerbating a cough (diagnosed with COPD).
- In November 2003 he lost balance while standing and broke hip, but was able to undergo surgery and is doing well...

Case Presentation 2

<table>
<thead>
<tr>
<th>Initial Visit</th>
<th>4+ year visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyzaar 50/12.5mg bid</td>
<td>1. Aspirin EC 81mg po qd</td>
</tr>
<tr>
<td>Coumadin</td>
<td>2. Coumadin</td>
</tr>
<tr>
<td>Simvastatin 40mg daily</td>
<td>3. Metoprolol succinate 200mg po qd</td>
</tr>
<tr>
<td>Insulin</td>
<td>4. Furosemide 40mg po qd</td>
</tr>
<tr>
<td></td>
<td>5. Digoxin 0.125mg po qd</td>
</tr>
<tr>
<td></td>
<td>6. Fedolipine 10mg po qd</td>
</tr>
<tr>
<td></td>
<td>7. Spironolactone 25mg po qd</td>
</tr>
<tr>
<td></td>
<td>8. Simvastatin 80mg po qd</td>
</tr>
<tr>
<td></td>
<td>9. Niaspan 2000mg po qam</td>
</tr>
<tr>
<td></td>
<td>10. NTG SL prn chest pain</td>
</tr>
<tr>
<td></td>
<td>11. Irbesartan 300mg po qd</td>
</tr>
<tr>
<td></td>
<td>12. Levetiracetam 0.15mg po qd</td>
</tr>
<tr>
<td></td>
<td>13. Fluphenazine decanoate</td>
</tr>
<tr>
<td></td>
<td>14. Loratadine 10mg po qd</td>
</tr>
<tr>
<td></td>
<td>15. Donepezil 5mg po qhs for memory</td>
</tr>
<tr>
<td></td>
<td>16. Citonapride 40mg po qam</td>
</tr>
<tr>
<td></td>
<td>17. Insulin 50% as directed</td>
</tr>
<tr>
<td></td>
<td>18. Insulin Regular as directed</td>
</tr>
<tr>
<td></td>
<td>19. Ipratropium 2 prn po qd</td>
</tr>
<tr>
<td></td>
<td>20. Lorazepam 0.5mg po bid prn anxiety</td>
</tr>
</tbody>
</table>

ACC / AHA 2005

Recommendations for Patients at High Risk of Developing HF (Stage A)

Class I
1. Control of systolic and diastolic hypertension (LOE: A)
2. Treatment of lipid disorders (LOE: A)
3. Control of blood sugar in patients with diabetes (LOE: C)
4. Control other risk factors (e.g., smoking, alcohol, drugs) (LOE: C)
5. Control of ventricular rate or restoration of NSR in supraventricular arrhythmias (LOE: B)
6. Treatment of thyroid disorders (LOE: C)
7. Periodic evaluation for signs and symptoms of HF (LOE: C)
8. If known ASCVD follow secondary prevention guidelines (LOE: C)
9. Non-invasive test of LVEF if family history of cardiomyopathy or receiving cardiotoxic interventions (LOE: C)

ACC / AHA 2005

Recommendations for Patients at High Risk of Developing HF (Stage A)

Class Ha
1. ACEI can be useful to prevent HF in patients with history of ASCVD, DM, or HTN associated with CV risk factors (LOE: A)
2. All blockers can be useful to prevent HF in patients with history of ASCVD, DM, or HTN associated with CV risk factors (LOE: C)

Class III
1. Routine use of nutritional supplements solely to prevent the development of structural heart disease
**ACC / AHA 2005**

**Drug Recommendations for Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed HF Symptoms (Stage B)**

**Class I**
1. All Class I recommendations for Stage A
2. BB and ACE inhibition in patients with previous AMI regardless of LVEF or presence of HF (LOE: A)
3. Beta-blockade in patients with no history of MI who have a reduced LVEF with no symptoms of HF (LOE: C)
4. ACE inhibition in patients with no history of MI who have a reduced LVEF with no symptoms of HF (LOE: A)
5. AI blocker in patients with previous MI without HF who are intolerant to ACEi and have a reduced LVEF (LOE: B)

**Class IIa**
1. ACE or AI blocker can be beneficial in hypertensive patients with LVH and no symptoms of heart failure (LOE: B)
2. AI blocker can be beneficial in patients with reduced LVEF and no symptoms of HF who are ACEi intolerant (LOE: C)

**Class III**
1. Digoxin should not be used in patients with low EF, NSR, and no history of HF symptoms (LOE: C)
2. Use of nutritional supplements to treat structural heart disease or prevent the development of symptoms of HF (LOE: C)
3. Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (LOE: C)

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**Drug Recommendations for Patients With Current or Prior Symptoms of HF (Stage C)**

**Class I**
1. Class I recommendations for Stage A and B patients
2. Diuretics and salt restriction in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (LOE: C)
3. ACE inhibitors for all patients with current or prior symptoms of HF and reduced LVEF unless contraindicated (LOE: A)
4. Beta-blockers (bisoprolol, carvedilol or metoprolol succinate) for all stable patients with current or prior symptoms of HF and reduced LVEF unless contraindicated (LOE: A)
5. AI blockers approved for the treatment of HF for all patients with current or prior symptoms of HF who are ACE inhibitor intolerant (LOE: A)
6. Avoidance or withdrawal of drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF (e.g. NSAIDs, most CCA, most antiarrhythmic drugs) (LOE: B)
7. Aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored (LOE: B)

**Class IIa**
1. AII blockers are reasonable as alternatives to ACE inhibitors as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking AII blockers for other indications (LOE: A)
2. Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (LOE: B)
3. Combination of hydralazine and nitrate is reasonable for patients with reduced LVEF who are already taking ACE inhibitor and BB for symptomatic HF and have persistent symptoms (LOE: A)

**Class IIb**
1. Combination of hydralazine and nitrate might be reasonable for patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACE inhibitor or AII blocker because of drug intolerance, HOTN, or renal insufficiency (LOE: C)
2. Addition of AI blocker may be considered in persistently symptomatic patient with reduced LVEF who are already being treated with conventional therapy (LOE: B)

**Class III**
1. Routine combined use of ACE inhibitor, AI blocker, and aldosterone antagonist is not recommended for patient with current or prior symptoms of HF and reduced LVEF (LOE: C)
2. CCA for routine treatment of HF in patients with current or prior symptoms of HF and reduced LVEF (LOE: A)
3. Long-term infusion of a positive inotropic drug may be harmful and is not recommended except as palliation for patients with end-stage disease who cannot be stabilized with standard medical therapy (LOE: C)
4. Use of nutritional supplementation as treatment for HF (LOE: C)
5. Hormonal therapy other than to replete deficiencies (LOE: C)

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**Drug Recommendations for Patients With Refractory End-Stage HF (Stage D)**

**Class IIb**
1. Continuous IV infusion of positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF (LOE: C)

**Class III**
1. Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF (LOE: B)