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

- Define heart failure and review the staging and NYHA classification of heart failure
- Discuss the epidemiology and economics of chronic heart failure
- Review recent data on pharmacologic agents used to treat chronic heart failure
  - Emphasis on dose optimization and monitoring
- Interactively apply the above via case examples

Definition of Heart Failure

“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

So, what is a clinical syndrome?
Other Definitions of Heart Failure

“ 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

SUPPLY ≠ DEMAND

Pathogenesis & Sequelae of HF

Common Causes in the Western World

1- Coronary artery disease
2- Hypertension
3- Valvular heart disease
4- Dilated cardiomyopathy
Diagnosis

• Clinical diagnosis based on careful history and physical examination
• It is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination
• Heart failure IS NOT equivalent to cardiomyopathy or LV dysfunction (i.e. low EF); these latter terms describe structural or functional reasons for the development of heart failure

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, S₄, laterally displaced apical impulse, pulmonary crackles or wheezes, hepatomegaly, peripheral edema
**Framingham Criteria for Dx of Heart Failure**

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

**Major criteria:**
- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to rx (major or minor)

**Minor criteria:**
- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Tachycardia (heart rate>120 beats/min.)

Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

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**Classifications of Heart Failure**

- **Heart failure with abnormal systolic function** a.k.a. heart failure with reduced LVEF
- **Heart failure with preserved systolic function** a.k.a. heart failure with a preserved ejection fraction
  - Although not truly equivalent, this classification considers normal systolic function and normal ejection fraction to be the same

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.


Patient Case

You are preparing for patients on rotation and are told by another student that your next patient is a 56yo wm with a history of coronary artery disease, diabetes, and hypertension who recently had an echocardiogram (ECHO) which revealed an ejection fraction of 30%.

Does this patient have heart failure?
Diagnosis

- Clinical diagnosis based on careful history and physical examination
- It is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination
- Heart failure IS NOT equivalent to cardiomyopathy or LV dysfunction (i.e. low EF); these latter terms describe structural or functional reasons for the development of heart failure

Aggravating Factors

- Medications (i.e. NSAIDS, Glitazones, certain chemotherapeutic agents)
- New heart disease or myocardial ischemia
- Arrhythmias (atrial fibrillation)
- Hypo/hyperthyroidism
- Infections
- Thromboembolism
- Dietary excess
- Physical inactivity
- Obesity
- Hypertension
- Endocarditis
- Pregnancy
Patient Case

You are working at a local pharmacy store for intern hours and a patient comes to pick up prescriptions for carvedilol, furosemide, digoxin, and lisinopril. The patient also has several cans of V-8 juice for checkout at the register.

Do you intervene, and how?

Patient Case

You are on rotation and the medical student on your team requests a recommendation for pain control in a 65yo black female with a history of heart failure and degenerative joint disease of both knees not satisfactorily relieved with acetaminophen or physical therapy. She declines invasive therapies (i.e. injections or surgery).

You recommend?
AHA Scientific Statement Use of Nonsteroidal Antiinflammatory Drugs

Stepped approach to pharmacologic therapy for musculoskeletal symptoms in patients with known CVD or risk factors for IHD (in order of preference).

– Acetaminophen, ASA, tramadol, or narcotic analgesics (short term)
– Nonacetylated salicylates
– Non COX-2 selective NSAIDs
– NSAIDs with some COX-2 selectivity
– COX-2 selective NSAIDs


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

Heart Disease and Stroke Statistics — 2006 Update. Dallas, Tx.: American Heart Association; 2005.
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

American Heart Association. 2006 Heart and Stroke Statistical Update. Dallas, Tx.: American Heart Association, 2005

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>70%</td>
<td>57%</td>
</tr>
<tr>
<td>1950-1969</td>
<td>41%</td>
<td>28%</td>
<td>75%</td>
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<td>28%</td>
<td>24%</td>
<td>59%</td>
<td>45%</td>
</tr>
<tr>
<td>1990-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td></td>
<td>38%</td>
<td>37.3%</td>
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<tr>
<td>Colon Cancer</td>
<td></td>
<td></td>
<td>38.6%</td>
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</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

- 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


Economic Burden
(estimated direct costs for 2006: 26.8 billion)

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

Goals of Therapy

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

AHA / ACC HF guidelines 2001
http://www.americanheart.org/presenter.jhtml?identifier=11841

Symptomatic Heart Failure: Just the Tip of the Iceberg

Gregg C. Fonarow, MD, Heart Failure: Scope of the Problem, Heart Failure University PowerPoint Presentation. Los Angeles, California, November 12-14, 2004.
Treatment: Non Pharmacologic

- Maintenance of fluid balance (sodium restriction ≤ 3 grams/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 (cardiac resynchronization therapy)
- 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
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- AT1 Receptor
- Renin
- ACE
- Bradykinin
- Inactive Peptides
- Chymase
- CAGE
- t-PA
- Cathepsin G
- Cathepsin G
- t-PA

ACE Pathways
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- ACE
- Bradykinin
- Inactive Peptides
- AT1 Receptor
- AT2 Receptor
- AT2 Receptor

ACE-I Pathways
- Antihypertrophic, proapoptotic ???
- Aldosterone Antagonists
- Beta-Blockers
- Thiazide and Loop Diuretics
- Sodium & Fluid Retention
- Thirst Stimulation
- Vasoconstriction
- Cell Growth
- Vagal Inhibition
- Sympathetic Activation
- Aldosterone Release
- Beta-Blockers

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"
Diuretics

- Only drugs in heart failure that can effectively control fluid retention
- Essential for symptomatic fluid overload
- Only class of drugs with a ACC/AHA Class I recommendation for HF with preserved ejection fraction
- Have not demonstrated a survival benefit

Sodium Reabsorption Sites in the Nephron

- 70% Proximal Tubule
- 5% Distal Tubule
- 20% Loop of Henle
- 1-4% Collecting Tubule

- Glomerulus
- Thiazide Diuretics
# Commonly Used Diuretics in Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption (%)</th>
<th>t½ (hr)</th>
<th>Relative Potency</th>
<th>Elimination</th>
<th>Initial daily dose (max daily dose)</th>
<th>Duration of action (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>~65%</td>
<td>~47</td>
<td>1</td>
<td>65% R</td>
<td>12.5-25mg (100mg)</td>
<td>24-72</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10% B, 25% U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTZ</td>
<td>~70%</td>
<td>~2.5</td>
<td>1</td>
<td>R</td>
<td>25mg (200mg)</td>
<td>6-12</td>
</tr>
<tr>
<td>Metolazone</td>
<td>~65%</td>
<td>4-5</td>
<td>10</td>
<td>80% R,</td>
<td>2.5mg (20mg)</td>
<td>12-24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10% H, 10%B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>~80%</td>
<td>~0.8</td>
<td>40</td>
<td>62% R 38% H</td>
<td>0.5-1mg * (10mg)</td>
<td>4-6</td>
</tr>
<tr>
<td>Furosemide</td>
<td>~60%</td>
<td>~1.5</td>
<td>1</td>
<td>65% R 35% H</td>
<td>20-40mg * (600mg)</td>
<td>6-8</td>
</tr>
<tr>
<td>Torsemide</td>
<td>~80%</td>
<td>~3.5</td>
<td>3</td>
<td>20% R 80% H</td>
<td>10-20mg (200mg)</td>
<td>12-16</td>
</tr>
</tbody>
</table>

HCTZ = Hydrochlorothiazide, * once or twice a day

Advantages: Loop Diuretics

- **Primary site of action: thick ascending limb**
  - Site of greatest Na⁺ capacity (25% of filtered Na⁺ load)
  - Nephron segments past this site do not possess reabsorptive capacity to reabsorb this rejectate
- **Effective despite low GFRs**
  - Basal level of fractional sodium reabsorption higher
  - Block tubuloglomerular feedback response (thiazides do not, and may enhance this at times)
Advantages: Thiazide Diuretics

- Better antihypertensives than loop diuretics
- Supported by hard outcome data in hypertensive patients
  - Long-term reduction in vascular resistance
- Less electrolyte disturbances
- Attractive in mild heart failure particularly if concomitant hypertension

Chronic Diuretic Use in Heart Failure: A Concern?

Chronic Diuretic Use in Heart Failure: A Concern?


Diuretics

- **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

Diuretics

• Initiation and Maintenance
  – 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


Determinants of Diuretic Response

Diuretic Resistance

- Noncompliance (medication, diet, fluid)
  - Salt excretion > 100mmol/day with no weight loss
- Drug interactions (NSAIDs, OAT inhibitors)
- Decreased renal delivery of drug or Na+
  - Optimize dose and if applicable the BP
- Absorption abnormalities (reduced/delayed peaks)
  - Administer in fasting state, trial with torsemide, posture post administration
- Hypertrophy of distal nephron
- Rebound Na+ uptake after volume loss

Diuretic Resistance

- Sequential nephron blockade
- Intravenous administration
  - Continuous intravenous (IV) infusion
    - Furosemide 40mg IV load, then 10-40mg/hr
    - Bumetanide 1mg IV load, then 0.5-2mg/hr
    - Torsemide 20mg IV load, then 5-20mg/hr
- Ultrafiltration
Which of the following are reasonable options in a patient with refractory edema (HF with low EF) on furosemide 80mg twice daily?

1. Change to bumetanide
   2mg bid
2. Add metolazone 5mg bid
3. Add metolazone qam
4. A or C

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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


DIG Trial: Analysis of Digoxin Levels

DIG Trial: Analysis of Digoxin Levels

- 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


A primary care colleague inquires what to do with a patient (HF with low EF in NSR) who has a digoxin level of 2.8ng/ml. Level was obtained at 10am, pt takes all medications at one time upon arising.

1. Continue current dose
2. Reduce dose to target a level < 1ng/ml and repeat level in 1-2 weeks
3. Reduce dose to target a level < 1ng/ml and repeat level in 1-2 days
4. Repeat level
Digoxin

- Initiation and Monitoring
  - Low doses of 0.125mg to 0.25mg daily
  - Pertinent PK/PD issues
    - Mostly renally eliminated
    - Half-life
    - Distribution and levels
  - Baseline level and again if changes in clinical condition, suspicion of toxicity, changes in renal function, addition of interacting drug (i.e. amiodarone)

Digoxin

- Adverse Reactions
  - Heart block
  - CNS (dizziness, visual disturbances, confusion, weakness)
  - Dermatologic: rash (1.6%)
  - Gastrointestinal: nausea, vomiting, diarrhea
  - Others: Increased estrogen levels, impotence
Beta-blockers and Heart Failure

• **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
  – Inhibition of sympathetically mediated vasconstriction

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

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
Which of the following is not a clinically important consideration when selecting beta-blocker therapy?

1. Cardioselectivity
2. Lipid solubility
3. Intrinsic sympathomimetic activity
4. Membrane stabilizing activity
5. All are equally important considerations

Characteristics of Beta-blockers

- Selectivity
  - Cardioselective: $\beta_1$
  - Not cardioselective: $\beta_1$, $\beta_2$
  - Ancillary receptor blockade: $\alpha_1$
- Intrinsic Sympathomimetic Activity (ISA)
  - Not desirable in ischemic patients
- Membrane Stabilizing Activity (MSA)
  - Stabilize action on action potential
    - High doses
    - Important experimentally, but not relevant to clinical management of arrhythmias
- Lipid Solubility
  - May play a role in side effects and tolerability
Beta Blocking Agents

Non-Selective
- ISA
Nadolol
Propranolol
Timolol
Sotalol

Selective*
- ISA
Atenolol
Metoprolol
Esmolol
Betaxolol
Bisoprolol
Nebivolol

+ ISA
Pindolol
Carteolol
Penbutolol

Selective
- ISA
Acebutolol
Celiprolol

+ ISA
Labetalol
Carvedilol
Bucindolol

*Beta-1 Cardioselective

Adapted from ESC Expert Consensus Document on B-adrenergic Receptor Blockers. Eur Heart J 2004;25;1341-1362

Beta-adrenergic Blocking Therapy
All-Cause Mortality in HF with reduced LVEF

RR

34%  $P = 0.0001$  CIBIS-II 1.3 years
placebo 228/1320 (17%)  bisoprolol 156/1327 (12%)

34%  $P = 0.0062$  MERIT-HF 12 months
placebo 217/2001 (11%)  metoprolol-XL 145/1990 (7%)

35%  $P = 0.0014$  COPERNICUS ~ 12 months
placebo 190/1133 (18.5%)  carvedilol 130/1156 (11.4%)

**Beta-adrenergic Blocking Therapy**

All-Cause Mortality in HF with reduced LVEF

- **Bucindolol**
  - ISA?
  - Decrease in NE release by pre-synaptic $B_2$ blockade lowering cardiac sympathetic drive (i.e. moxonidine)
  - Gly-389 carriers versus Arg-389 carriers

- **Metoprolol tartrate immediate release**
  - COMET trial
  - Choice of dose?, choice of regimen?
  - Differential effects on heart rate and blood pressure?
  - Differences in receptor onset/offset kinetics, duration of action, and inverse agonism in favor of carvedilol?

**Bottom line:** All dosage forms and all beta-blockers are not interchangeable in the treatment of heart failure with reduced left ventricular ejection fraction


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**The Failing Heart and Adrenergic Receptors**

- **Dominant receptor in normal human heart is Beta-1**
- **In the failing heart ratios change**
  - 40% beta-2
  - 10% alpha-1 (up regulated)
  - 60% beta-1 (down regulated)

The Failing Heart and Adrenergic Receptors

- However, you need to consider both selectivity of the neurohormones that stimulate these receptors and pathogenic consequences of specific receptor stimulation

  - The signaling molecule that drives adrenergic receptors that is increased in the failing heart is norepinephrine
    - 20:1 affinity for beta-1 versus beta-2
    - 10:1 affinity for beta-1 versus alpha-1

  - Myopathic potential appears much greater with beta-1 stimulation versus beta-2
    - 10x stimulation of beta-2 receptor to get the same degree of cardiomyopathy seen with stimulation of beta-1 receptor


Initiation and Monitoring of Beta-Blockers

Stable on ACE? (i.e. no IV inotropes or s/sx's of fluid)
- Initiate BB at lowest dose
- Double dosage q 2 wks to achieve doses known to reduce mortality
- Well tolerated?
  - Yes
  - No

Hypotension?
- ↓ vasodilator/ACEI/diuretic Space doses

Worse HF? (edema, SOB)
- ↑ Diuretic/ACEI
- ↓ BB if necessary

Bradycardia?
- ↓ to last tolerated BB dose
- Adjust other meds

Other? (fatigue, impotence)
- Educate
- Adjust BB dose

# Beta-blockers

<table>
<thead>
<tr>
<th>Beta-blockers w/proven mortality benefit in HF with low LVEF</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25mg once daily</td>
<td>10mg once daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.215mg twice daily</td>
<td>25mg twice daily*</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5 to 25mg once daily</td>
<td>200mg once daily</td>
</tr>
</tbody>
</table>

* 50mg twice daily if patient more than 85kg


## Why titrate the Beta-blocker?

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<td>1990-1999</td>
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<td></td>
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<tr>
<td>All Cancer</td>
<td></td>
<td></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

Beta-blockers

• Contraindications
  – Second or third heart block
  – Sinus bradycardia
  – Sick sinus syndrome

• Precautions
  – Asthma
  – Severe peripheral arterial disease
  – Uncompensated cardiac failure

---

Beta-blockers

• Other Adverse Reactions
  – Cold peripheries
  – Bronchoconstriction
  – Interference with autonomic and metabolic responses to hypoglycemia
Renin-Angiotensin-Aldosterone System

**Non ACE Pathways**
- t-PA
- Cathepsin G
- Chymase
- CAGE

**ACE Pathways**
- Angiotensinogen
- Renin
- Angiotensin I
- ACE
- Angiotensin II
- ACE-I
- Inactive Peptides
- Bradykinin

**AT1 Receptor**
- AT1 Receptor
- Antihypertrophic, proapoptotic ???

**AT2-4 Receptors**
- AT2-4 Receptors
- Sodium & Fluid Retention
- Aldosterone Release
- Sympathetic Activation

**Actions of Circulating & Tissue RAS**

**Circulating Renin-angiotensin System (30%)**
- Short-term Effects
  - Sodium and water reabsorption
  - Kidney
  - Vessels
  - Vasoconstriction
  - Heart
  - Positive inotropic, chronotropic and arrhythmogenic effects

**Tissue Renin-angiotensin System (70%)**
- Long-term Effects
  - Kidney
  - Intraglomerular hypertension
  - Vessels
  - Vascular hypertrophy
  - Myocardial hypertrophy
  - Heart

Dzau 1989
**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)

- **Populations studied**
  - Systolic dysfunction (EF $\leq$ 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 $< 90$mmHg, moderate renal insufficiency (serum creatinine $> 2.5$mg/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)

- **Initiation and Maintenance**
  - Low doses with K+ and renal function checked within 1 to 2 weeks and periodically after
  - Titrated as tolerated to doses demonstrated to provide a clinical benefit or to moderate-high to high doses
    - Studies evaluating ACE-I titrated to a target dose NOT therapeutic response
    - Studies evaluating other drugs on top of ACE-I usually had at least intermediate doses of ACE-I given
  - Concurrent diuretic therapy may need to be adjusted initially or after therapy started
  - 85 to 90% of patients can tolerate short- and long-term therapy

Angiotensin Converting Enzyme Inhibitors (ACE-I)

• **Contraindications**
  – Bilateral renal artery stenosis
  – Unilateral stenosis of single functional kidney
  – Angioedema
  – Pregnancy (2\textsuperscript{nd}, 3\textsuperscript{rd} trimester)
  – $K^+ \geq 5.5$ mmol/L that cannot be reduced

• **Precautions**
  – Renal impairment (Creatinine $\geq 3$mg/dL)
  – Systolic blood pressure $< 80$mmHg

Angiotensin Converting Enzyme Inhibitors (ACE-I)

• **Adverse Reactions**
  – Angioedema ($<1\%$, more frequent in blacks)
  – Hyperkalemia
  – Hypotension
  – Cough ($5$-$10\%$, up to $50\%$ of Chinese)
  – Renal insufficiency ($5$-$30\%$ incidence of increase in serum creatinine of $> 0.3$mg/dl)
  – Rash
  – Taste disturbance
  – Other
# 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><strong>Benazepril (Lotensin®)</strong></td>
<td>Not FDA approved</td>
<td>80mg</td>
</tr>
<tr>
<td><strong>Captopril (Capoten®)</strong></td>
<td>50mg three times daily</td>
<td>450mg</td>
</tr>
<tr>
<td><strong>Enalapril (Vasotec®)</strong></td>
<td>10-20mg twice daily</td>
<td>40mg</td>
</tr>
<tr>
<td><strong>Fosinopril (Monopril®)</strong></td>
<td>40mg daily</td>
<td>80mg</td>
</tr>
<tr>
<td><strong>Lisinopril (Zestril®, Prinivil®)</strong></td>
<td>20-40mg daily</td>
<td>80mg</td>
</tr>
<tr>
<td><strong>Moexipril (Univasc®)</strong></td>
<td>Not FDA approved</td>
<td>30mg</td>
</tr>
<tr>
<td><strong>Perindopril (Aceon®)</strong></td>
<td>Not FDA approved</td>
<td>16mg</td>
</tr>
<tr>
<td><strong>Quinapril (Accupril®)</strong></td>
<td>40mg twice daily</td>
<td>80mg</td>
</tr>
<tr>
<td><strong>Ramipril (Altace®)</strong></td>
<td>10mg once daily</td>
<td>20mg</td>
</tr>
<tr>
<td><strong>Trandolapril (Mavik®)</strong></td>
<td>4mg daily</td>
<td>8mg</td>
</tr>
</tbody>
</table>


Does Dose Optimization Matter?
The Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial

- 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=0.374)
- Post-hoc analysis
  - 15% in combined all-cause mortality and hospitalization for heart failure (p<0.001)

<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.


**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

Astra-Zeneca  http://www.cardio.net
AII Receptor Blockers

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

AII 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
AII 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

Dosing of ARBs in LV Dysfunction Trials

• ARB with an ACE-I
  – ValHeFT (heart failure) : Valsartan 160mg bid (254mg avg. daily dose) added to mean daily dose of captopril of 80mg
  – CHARM-Added (heart failure): Candesartan 32mg qd (24mg avg. daily dose) added to mean daily dose of captopril of 82mg
  – VALIANT (post MI heart failure): Valsartan 160mg bid (247mg avg. daily dose) vs. captopril 50mg tid (117mg avg. daily dose) vs. combination of valsartan 80mg bid (116mg avg. daily dose) PLUS captopril 50mg tid (107mg avg. daily dose)

In ValHeFT and CHARM where benefit was seen when high dose ARB was added to ACE-I, the dose of ACE-I was modest
In VALIANT where no benefit was seen when ARB added to ACE-I, the dose of ACE-I was high and the dose of ARB modest
ACE Inhibitors and AII Receptor Antagonists

- ACE inhibitors remain the cornerstone of anti-RAS type therapy in HF with low EF
- ACEi or AII receptor antagonists can be used in CKD
- AII receptor antagonists are alternatives to ACE inhibitors as 1st line therapy
- Combinations of both may be considered in select heart failure patients with close monitoring (no mortality benefit, and data is equivocal)

You initiate an ACEi on a patient with HF with low EF who also has CKD. After one week the estimated GFR has decreased by 20%. You do the following?

1. Stop the ACEi, repeat labs in 1-2 weeks
2. Continue dose, repeat labs in 1-2 weeks
3. Reduce dose, repeat labs in 1-2 weeks
4. Refer the patient to nephrology
Monitoring Renal Function

<table>
<thead>
<tr>
<th>Table 137. Changes in Management Based on Magnitude of Early Decrease in GFR</th>
<th>0-15%</th>
<th>15-30%</th>
<th>30-50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage adjustment for ACEI and ARBs</td>
<td>None</td>
<td>None</td>
<td>Reduce</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Recommended interval for monitoring GFR</td>
<td>As per GFR (previous table)</td>
<td>Once after 10-14 days, if creatinine GFR remains within 15-30% of baseline value, resume monitoring schedule as per GFR (previous table)</td>
<td>Every 5-7 days until GFR is within 30% of baseline value</td>
<td>Every 5-7 days until GFR is within 15% of baseline value</td>
</tr>
<tr>
<td>Evaluate for causes of decreased GFR (including consideration of RAD, see Guideline 4)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Monitoring Serum Potassium

| Table 142. Recommendations for Prevention and Management of Hyperkalemia, According to Baseline Serum Potassium (mEq/L) |
|---|---|---|---|---|
| Baseline Serum Potassium (mEq/L) | ≤4.5 | 4.5-5.0 | 5.1-5.5 | >5.5 |
| Education to avoid high potassium foods | No | Yes | Yes | Yes |
| Measures to lower serum potassium | No | No | Simultaneous with initiation | Prior to initiation |
| Recommended interval for monitoring serum potassium after initiation or change in dose of antihypertensive therapy | 4-12 weeks | 2-4 weeks | ≤2 weeks | ≤2 weeks |

Aldosterone Inhibitors

Spironolactone

Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

- Retention Na+
- Retention H$_2$O
- Excretion K$^+$
- Excretion Mg$^{2+}$

Edema

Arrhythmias

Collagen deposition

Fibrosis
  - myocardium
  - vessels

ALDOSTERONE

Aldosterone Antagonists

- Mechanism of action
  - Block aldosterone binding at mineralcorticoid receptors in kidney, heart, blood vessels, and brain (competitive antagonists)
  - Blockade of aldosterone in distal renal tubule $\rightarrow$ increased Na$^+$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
  - Ongoing trials: TOPCAT, EMPHASIS-HF

Aldosterone Antagonists

– In the EPHESUS trial eplerenone was 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)


Pharmacologic Considerations with Aldosterone Antagonists

Selectivity
– Eplerenone 1000x less binding to androgen receptor, 100x less to progesterone receptor, and 10-20x less to mineralcorticoid receptor, yet still 50-75% as potent as spironolactone

Administration with food
– Eplerenone (no effect), spironolactone (increased absorption)

Metabolites
– Eplerenone (inactive), spironolactone (active + long half-life)

Metabolism/drug interactions
– Eplerenone (CYP 3A4 interactions)

Aldosterone Antagonists

- Exclusions from heart failure studies
  - Serum creatinine > 2.5mg/dL
    - 95% of patients in RALES had serum creatinine 1.7mg/dl or less
  - Serum potassium > 5.0 mEq/L
    - Incidence of K+ > 6mEq/L in EPHESUS of 10% if baseline CrCl < 50ml/min
- 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


Aldosterone Antagonists

- 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
- Listed contraindications in HF (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
- Vent. Wall stress
- MVO₂

2- Coronary vasodilatation

- Myocardial perfusion

3- Arterial vasodilatation

- Afterload

4- Others

Cardiac output
Blood pressure
Hydralazine/ISDN

• Achievement of both arterial and venous vasodilation
  – Nitrates may also inhibit abnormal myocardial and vascular growth
  – Hydralazine may interfere with some biochemical and molecular mechanisms responsible for progressive HF
  – Hydralazine may inhibit development of nitrate tolerance
• Phenotype vs genotype predicted responses
  – A-HeFT Genetic Risk Assessment in Heart Failure substudy (GRAHF)
  – T haplotype (TT) vs C haplotype (TC or CC) of the GNB3 gene

Nitrates + Hydralazine

Probability of Death

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

0 6 12 18 24 30 36 42

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

Placebo (273)
Prazosin (183)
Hz + ISDN (186)

23% reduction in mortality at 3 years
Nitrate + Hydralazine

Probability of death

V-HeFT II

Hydralazine/Isosorbide Dinitrate

Hydralazine/Isosorbide Dinitrate

Target dose (daily): 225mg hydralazine; ISDN 120mg

A-HeFT

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
    - Diltiazem or verapamil may be useful in chronic heart failure with preserved ejection fraction
  - 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 benefit)
  - 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 in some studies, but no mortality benefit, when added to other agents)
Pharmacologic Management of Heart Failure with Preserved (Normal) Ejection Fraction

- Lack of controlled clinical trials
- Focus on control of physiological factors
  - Blood pressure, heart rate, blood volume
  - Myocardial ischemia
- Angiotensin II Receptor blockers
  - CHARM PRESERVED (EF > 40%) showed a trend with candesartan to a reduction in primary end point of CV death and HF hospitalizations of 9%, which was nonsignificant in the unadjusted analysis but had a p value of 0.051 when adjusted for 33 prespecified baseline variables (the reduction was mostly in hospitalizations)
  - I-PRESERVE (EF ≥ 45%) did not show any benefit with irbesartan in the primary or any endpoint or subgroup.

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)
Pharmacogenomics and Beyond…

• Traditional trials: shotgun (depersonalized) approach
• Response to therapy and genotype/polymorphisms
  – ACE D/I genotypes
  – β 1 Ser49Gly, Gly389Arg
  – β 2 Arg16Gly, Gln27Glu, Thr164Ile
  – NOS3 Genotypes
• Metabolomics
• Proteomics
• Transcriptomics

Heart Failure Case 1

• 82 y/o white male new to the clinic presents with a history of heart failure (EF 30%), AICD/PM, CAD (post MI 1995), HTN, Dyslipidemia, DM, PAD with intermittent claudication, chronic kidney disease.
• Currently, quite stable with no complaints. Able to do ADL without symptoms and no changes in medications in the last 18 months. No edema. No PND/Orthopnea. No dizziness or lightheadedness. No chest pain.
Heart Failure Case 1

- Medications: ASA 81 mg daily, carvedilol 25 mg bid, furosemide 80 mg daily, KCL 20 meq daily, enalapril 20 mg BID, simvastatin 40 mg HS, digoxin 0.25 mg daily, cilostazol 100 mg BID.
- BP 110/70 mmHg, pulse 56.
- BUN 30, Cr 1.6, GFR 44 ml/min, digoxin level 1.4 ng/ml, K+ 4.8 meq/L.

How would you approach this patient?

1. Re-evaluate current dose of furosemide
2. Re-evaluate digoxin dose
3. Discontinue cilostazol
4. All of the above
Heart Failure Case 2

- 62 y/o white female with chronic kidney disease, proteinuria, diabetes mellitus, hypertension, moderate LVH, obesity, and chronic heart failure with LV systolic dysfunction (EF 35%), NYHA Class II.
- Medications: metoprolol succinate 100 mg daily, bumetanide 2 mg daily, rosuvastatin 10 mg daily, aspirin 81 mg daily, digoxin 0.125 mg every other day.
- LAB: BUN 30, Cr 2.5 mg/dL, GFR 28 ml/min K+4.8 meq/L.
- BP 115/65 mmHg, HR 55 bpm.

What would you do?

1. Add ACE inhibitor
2. Add ARB
3. Neither
4. Both
Lisinopril 2.5mg daily was added. One week later her BUN increased to 32, and serum creatinine to 3 mg/dL.

What would you do?

1. Stop ACE inhibitor
2. Continue ACE inhibitor
3. Increase dose of ACE inhibitor
4. Decrease diuretic
5. Call your lawyer

Heart Failure Case 3

- A 73 y/o male with chronic heart failure with preserved ejection fraction (EF 55%) presents for follow up. Patient admits to dietary and medication noncompliance at times. He is currently NYHA Class II with symptoms predominately only if rushing or moving objects around up and down the stairs of his town home. He also complains of mild edema which resolves at night.
Heart Failure Case 3

- Medications: diltiazem SR 240 mg daily, furosemide 20 mg daily, captopril 50 mg TID, simvastatin 40 mg QHS, aspirin 81 mg daily.
- BP 160/70 mmHg, repeated 155/65 mmHg, HR 75 bpm.
- LAB: BUN 15, Cr. 1.2 mg/dL, GFR 63 ml/min.

How would you optimize his care?

1. Stop diltiazem as he has heart failure
2. Change furosemide to chlorthalidone
3. Change captopril to lisinopril 40 mg daily
4. Increase furosemide to 20 mg BID
5. A & D
6. B & C