Heart Failure Therapeutics

Harleen Singh Pharm.D.
Assistant Professor
OSU/OHSU COP
Management of Heart Failure
A major public health problem

- Approximately 5 million patients in the United States have HF
- Over 550,000 patients are diagnosed with HF for the first time each year
- Primary reason for 12 to 15 million office visits and 6.5 million hospital days each year
Heart Failure is Primarily a Condition of the Elderly

• The incidence of HF approaches 10 per 1000 population after age 65

• HF is the most common Medicare diagnosis-related group

• More dollars are spent for the diagnosis and treatment of HF than any other diagnosis by Medicare
Normal Heart Function

• “Ability to fill at low enough pressure not to cause congestion,
• then deliver a sufficient quantity of blood at high enough pressure for tissue perfusion,
• and augment this performance during exercise.”
Definition: Heart Failure

• Complex clinical syndrome resulting from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood.

• Manifested as symptoms of dyspnea and fatigue, and sometimes signs of fluid excess.

• Not all patients have volume overload
  – “heart failure” is preferred over CHF.
Practice Guidelines

- American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult
- First issued in 1995. Updates in 2001 and 2005
  - J Am College of Cardiology. Dec 2001
  - J. Am College of Cardiology. Sept 20, 2005
  - Circulation. Sept. 20, 2005
  - www.americanheart.org
Cardiovascular Physiology: Two Guiding Principles

- The most basic goal of all cardiovascular homeostasis mechanisms is to insure adequate perfusion of the kidneys and brain. All other organs will be sacrificed to this end, if need be, including the heart.
- When cardiovascular homeostasis is disturbed, the body will do 3 main things:
  1. vasoconstrict (to support BP and increase venous return)
  2. increase cardiac contractility
  3. expand intravascular volume
Concepts to understand

- Preload
  - Central venous pressure (CVP)
  - Pulmonary artery wedge pressure (PAWP)
- Afterload
- Contractility
Pre-load

- Clinically measured as the ventricular end-diastolic volume. Often approximated by end-diastolic pressure. (LVEDV)
- Forces on venous side affecting myocardial wall tension
- Central venous pressure; pulmonary artery wedge pressure
Afterload

- Tension developed in ventricular wall during systole
- Left ventricular outflow resistance; arterial impedance
- Elevated systemic vascular resistance (SVR)
- Ventricular Wall Stress: the formal definition of afterload. Wall Stress = (P x r)/2h. Often approximated by systolic blood pressure (assuming no valvular obstruction).
Contractility:

- **Contractility**: the intrinsic ability of the myocardium to shorten when preload and afterload are held constant.
Ejection fraction

- **EF = Percent** of left ventricular blood ejected during each systolic contraction. Surrogate of contractility.
  - Normal = 60%
  - EF = stroke volume
  - end-diastolic volume
  - “Low” = <40% (as low as 20% in severe HF)
  - Consider high ventricular volume with low contractility vs. low ventricular volume with normal contractility.
Stroke Volume

- Stroke volume (SV) = \textit{volume} of blood ejected during each systolic contraction. NI 60-130 mL
  - Function of contractility, LV end diastolic volume, “wall stiffness”, and mitral valve regurgitation.
- Cardiac output (CO) = SV \times HR. NI 4-7 L/min
Measuring Ejection Fraction

• Two dimensional echocardiography with Doppler flow (Doppler echocardiogram)
  – Also data on valvular functions; wall geometry, thickness, and motion of ventricles.
• Radionuclide left ventriculography
  – (MUGA: multiple gated acquisition scan)
  – More accurate EF, but no info on valves, function
• Left ventricular contrast angiography
Determinants of Cardiac Output

Fig. 9–2. Key mediators of cardiac output. Determinants of the stroke volume include contractility, preload, and afterload. Cardiac output = Heart rate × Stroke volume.
Cardiac Cycle

Diagram showing the cardiac cycle with key points labeled:
- Stroke volume
- Aortic valve closes; ESV
- Ventricular ejection
- Aortic valve opens
- Isovolumic contraction
- Mitral valve closes; EDV
- Right ventricular diastole + filling

Key points:
- A: End-diastolic volume
- ESV: End-systolic volume

Arrows indicate:
- A → B: Passive filling and atrial contraction
- B → C: Isovolumic contraction
- C → D: Ejection of blood into aorta
- D → A: Isovolumic relaxation
LV pressure – volume Relationship

LV Pressure-Volume Relationship during Diastole

LV Pressure (mmHg)

LV Volume (mL)

Slope = ΔP/ΔV
= Elastance
Effect of Increased Preload on LV Pressure – Volume Loop

Effect of Increased Preload on LV Pressure-Volume Loop

LV Pressure (mmHg)

LV Volume (mls)

End-systolic Pressure-volume line

Loop 2 has an increased preload (increased LVEDV) as compared to loop 1.
Note: Loop 2 has a larger stroke volume than loop 1.

The afterload & contractility have remained constant. The afterload lines for the 2 loops are parallel so they have the same afterload. Both end-systolic points are on the same contractility line so the 2 loops have the same contractility.
Effect of Increased Afterload on LV Pressure-Volume Loop

Note the decreased stroke volume for loop 2 (which has the increased afterload). The aortic valve is closing at a higher pressure so less volume is ejected during systole.
Effect of Increased Contractility on LV Pressure – Volume Loop

Note the increased stroke volume for loop 2 (which has the increased contractility).
* The increased slope of the end-systolic pressure-volume line is an index of the increased contractility.
* The end-systolic points of both loops lie on the same ‘afterload line’ so there afterload is the same for the 2 loops.
* The LVEDV is the same for the 2 loops so the pre-load is the same.
Frank-Starling Curves

• Relate preload (measured as LVEDP) to cardiac performance (stroke volume, SV)
• In normals, SV increases with LVEDP
• In Heart Failure, see very little SV increase with rising LVEDP
• At any LVEDP, increased contractility increases SV
Pathophysiology of HF

- Cardiorenal
- Hemodynamic model
- Neurohormonal model
- Genetic model

1950 - 2000
Pathophysiology of Heart Failure

Adverse Remodeling

- Primary Insult
  - Decreased Cardiac Performance
    - Neuchochemical Stimulation
      - Release of Renin/Angiotensin, Catecholamines, Others
        - Vasoconstriction, and Increased Vascular Volume
          - Increased Preload
            - Heart Failure Symptoms

- Increased Afterload
Major Compensatory Mechanisms in Heart Failure

- Frank-Starling Mechanism
- Ventricular Hypertrophy
  - concentric: wall thickening
  - eccentric: chamber dilation
- Adrenergic activation
- Renin-Angiotensin-Aldosterone activation
- Vasopressin (ADH) activation
Compensatory mechanisms
Cardiac Remodeling

- Consequence of adaptive mechanisms
- Altered geometry (shape and mass) of left ventricle
  - LV chamber dilation: “congestion” via retention of blood in ventricle. Spherical shape. Link to Starling Curve
  - Cardiac muscle hypertrophy: increased muscle mass, thickened LV wall
  - Fibrosis
- Also may be a direct effect of NE, angiotensin II, and aldosterone.
  - Consider consequences of using aldosterone inhibitors (spironolactone and eplerenone)
**A** Ventricular remodeling after acute infarction

- **Initial infarct**
- **Expansion of infarct (hours to days)**
- **Global remodeling (days to months)**

**B** Ventricular remodeling in diastolic and systolic heart failure

- **Normal heart**
- **Hypertrophied heart (diastolic heart failure)**
- **Dilated heart (systolic heart failure)**
Neuro-Hormonal Activation in HF
Renin-Angiotensin-Aldosterone System

- Reduced renal blood flow triggers renal renin release

- Angiotensin II is both a direct arterial vasoconstrictor and stimulant of aldosterone release from the adrenals
Other Compensatory Mechanisms

- **Endothelin** produced by endothelial cells, produces vasoconstriction
- Reduction in endothelium-produced **nitric oxide (EDRF)**, a vasodilator, leading to vasoconstriction
Natriuretic Peptides

- **A-type. Atrial natriuretic peptide (ANP)**
  - Secreted by the atrial myocardium in response to dilation (stretch)
- **B-type. Formerly “brain natriuretic peptide” (BNP)**
  - Produced by ventricle myocardium in response to elevations of end diastolic pressure and volume
  - Biochemical marker of presence of heart failure
    - >100 pg/mL to differentiate from other causes of dyspnea or edema (NEJM. July 18, 2002)
    - Degree of elevation correlates with severity (mean 241 pg/mL in NYHA class I; 817 pg/mL in Class IV)
  - Nesiritide (Natrecor): synthetic recombinant human BNP
- **C-type.**
  - Secreted by lung, kidney, heart and vascular endothelium in response to increased shear stress. Minimal diuretic effect.
Naturetic Peptide for Diagnosis of CHF

- In 1586 pts with acute dyspnea:
- Blood level > 100 pcg/ml: 83% sensitive
- Blood level < 50 pcg/ml: 96% specific
- Better than any other clinical predictor

Compensatory mechanisms

• Helpful early in disease; harmful later
• Sympathetic nervous system activation
  – \( \uparrow \text{NE} \rightarrow \) vasoconstriction, tachycardia, increased contractility
  – Decreased beta\(_1\) receptor number and sensitivity; relative over response of beta 2 receptors (termed “receptor uncoupling”)
  – Greater susceptibility in African Americans?
• Renin-angiotensin-aldosterone activation
  – vasoconstriction, sodium retention (edema)
  – Aldosterone and angiotensin II may directly lead to heart cell damage and remodeling
Etiology of heart failure

- Ischemic/coronary artery disease (2/3)
  - Includes post MI
- Non-ischemic cardiomyopathy
  - Hypertension (increased afterload): 75% of pts
  - Valvular dysfunction (aortic or mitral valve); includes post-streptococcal
  - Alcoholic or viral myocarditis, thiamine deficiency
- Idiopathic cardiomyopathy (e.g., thick intraventricular septum)
- Congenital malformations
- Sarcoidosis, amyloidosis, hemochromatosis
Other contributors to heart failure

- Endothelins (discussed under pulmonary hypertension)
- Arginine-vasopressin: free water retention, possible dilutional hyponatremia
- Cytokines
  - tissue necrosis factor (TNF $\alpha$)
  - Interleukin 6 (pro-inflammatory, impair LV contractility)
- Suppression of nitrous oxide due to reduced expression of endothelial NO synthase
Drug induced or aggravation of existing HF

- Anthracyclines (doxorubicin-Adriamycin) (plus trastuzumab)
- Antiarrhythmics (least with amiodarone)
- Beta blockers (non-selective)
- Calcium channel blockers except amlodipine (Norvasc), felodipine (Plendil)
- NSAID (sodium retention)
- Rosiglitazone (Avandia), pioglitazone (Actos) (sodium retention). Metformin: risk of lactic acidosis.
- Heroin or Ritalin. Lung damage, right sided failure
- Fenfluramine. Cor pulmonale/pulmonary HTN
- TNF antagonists: etanercept, infliximab
Classification of HF

• Low output

• High output failure. Hyperthyroidism
  – Overworked healthy heart due to high metabolic demand
Classification of HF

• Left Ventricle dysfunction

• Right ventricular dysfunction
  – Usually secondary to left sided failure (fluid back up through pulmonary circulation)
  – Isolated/primary right sided failure: pulmonary hypertension, cor-pulmonale (to be discussed later in lecture)
Systolic and Diastolic HF

• Systolic dysfunction. 60-70% of HF cases
  – Low EF (<40%) as cause of low CO
  – Classic “congestive heart failure” due to decreased contractility (“pump failure”).

• Diastolic dysfunction. 14-40% of cases
  – Normal EF (>45%), normal contractility, nl sized heart on CXR
  – “stiff” left ventricle (reduced wall compliance), inability of ventricle to relax during diastole, impaired LV filling, elevated resting pressure in ventricle despite low volume of blood being returned. Also rapid HR shortens duration of diastolic filling.
  – CO low because high fraction of low volume is ejected
### ACA/AHA Staging (2005)

<table>
<thead>
<tr>
<th>At Risk for Heart Failure</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Stage C</td>
</tr>
<tr>
<td>At high risk of HF but without structural heart disease or HF symptoms</td>
<td>Structural heart disease with prior or current HF symptoms</td>
</tr>
<tr>
<td>Stage B</td>
<td>Stage D</td>
</tr>
<tr>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
</tbody>
</table>
New York Heart Association (NYHA) Classification

- By functional disability
  - Class I
    - No limitations on normal physical activity; but symptoms with exertion (exercise)
  - Class II
    - Symptoms of HF with ordinary activity
  - Class III
    - Marked limitations in physical activity
      - Bathing, dressing
  - Class IV
    - Symptoms of HF at rest
ACC/AHA Classification of Recommendations

• **Class I:**
  – Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective

• **Class II:**
  – Conditions for which there is *conflicting* evidence and/or a *divergence of opinion* about the usefulness/efficacy of a procedure or treatment
  – **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy
  – **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion

• **Class III:**
  – Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful
ACC/AHA Level of Evidence

- **Level A**: Data derived from multiple randomized clinical trials or meta-analyses
- **Level B**: Data derived from a single randomized trial, or nonrandomized studies
- **Level C**: Only consensus opinion of experts, case studies, or standard-of-care
Symptoms of HF

- Shortness of breath (SOB)
- Cough
- Orthopnea
- Paroxysmal nocturnal dyspnea (PND)
- Dyspnea on exertion (DOE)
- Edema
- Fatigue
- Weight gain (anorexia may be seen in advanced HF)
Signs of HF

- Tachycardia
- Increasing weight
- Jugular venous distention (JVD)
- or hepatojugular reflux
- Presence of S3 (third heart sound)
- Laterally displaced apical impulse
- Pulmonary crackles or wheezes
- Hepatomegaly
- Peripheral edema
## Heart Failure
### Subjective Findings

<table>
<thead>
<tr>
<th>Left Ventricular Failure</th>
<th>Right Ventricular Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak, fatigue, confusion</td>
<td>Weak, fatigue, confusion</td>
</tr>
<tr>
<td>Shortness of Breath (SOB)</td>
<td>Edema (1+ to 4+)</td>
</tr>
<tr>
<td>Dyspnea on exertion (DOE)</td>
<td></td>
</tr>
<tr>
<td>Orthopnea (2-3 pillows)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea (PND)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
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</tbody>
</table>
# Heart Failure

## Objective Findings

<table>
<thead>
<tr>
<th>Left Ventricular Failure</th>
<th>Right Ventricular Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 min walking distance (Treadmill or home)</td>
<td>Weight gain (fluid retention)</td>
</tr>
<tr>
<td>Enlarged heart on XRay</td>
<td>Neck vein distension (Jugular Venous Distension)</td>
</tr>
<tr>
<td>EF &lt; 40%</td>
<td>Enlarged liver</td>
</tr>
<tr>
<td>Rales, S₃ gallop rhythm</td>
<td>&quot;Hepatojugular reflex&quot;</td>
</tr>
<tr>
<td>BP (hypotension)</td>
<td>Ascites (fluid in adomen)</td>
</tr>
<tr>
<td>Reflex tachycardia</td>
<td></td>
</tr>
<tr>
<td>↑ BUN (poor renal perfusion)</td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT OBJECTIVES

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

Myocardial Insult → ↓ LV Function

↑ Afterload

↑ Vasoconstriction

Na & H₂O Retention

↓ Cardiac Output

↓ Renal Perfusion

Neurohormone Activation

Progression of HF & Symptoms

Nonpharmacologic therapy of heart failure

• Dietary sodium and fluid restriction
  • limit Na intake to 1-3 g/day
  • limit fluids to <2 L/day

• Physical activity appears to improve functional status
Pharmacologic therapy

- Diuretics
- Digoxin
- ACEI
- ARBs
- Beta-Blockers
- Aldosterone Antagonists
Hemodynamic Effects of Therapies

- a to b: diuretic
- a to b': over-diuresis
- a to c: inotrope (dobutamine)
- a to d: mixed arterio-venous vasodilator (IV nitroprusside, oral ACE inhibitor)
- a to e: inotropic agent (dobutamine) plus vasodilator
Diuretics
Nephron

Diuretics
1. Acetazolamide
2. Osmotic agents (mannitol)
3. Loop agents (e.g., furosemide)
4. Thiazides
5. Aldosterone antagonists
6. ADH antagonists
Diuretics

- Thiazide diuretics
- Loop diuretics
- Metolazone
- Potassium sparing diuretics
Diuretics

• Place in therapy
  - Used for symptomatic relief
  - Rapid onset of action, but not recommended as monotherapy
  - PRN use, titrate to edema, SOB weight
Loop diuretics

- Why loop diuretics in HF?
- Which route? IV Vs oral
- Which drug and dose?
# Dosing loop diuretics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Usual Daily Dose</th>
<th>Ceiling Dose (total daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide (generic, Lasix)</td>
<td>20-160 mg (QD or BID)</td>
<td>80-160 mg (200 IV, 400 PO if Clcr &lt;20 ml/min)</td>
</tr>
<tr>
<td>Bumetanide (Bumex)</td>
<td>0.5-4 mg (QD or BID)</td>
<td>1-2 mg (8-10 mg if Clcr &lt;20 ml/min)</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
<td>10-80 mg (QD)</td>
<td>20-40 mg (100 mg if Clcr &lt;20 ml/min)</td>
</tr>
</tbody>
</table>

Furosemide: 20-40 mg → 80 mg → 120 mg → 180-240 mg → 400 mg
Diuretic resistance

• Diuretic resistance: inadequate clearance of edema despite a full dose of diuretic
## Diuretic resistance

<table>
<thead>
<tr>
<th>Cause or resistance</th>
<th>Therapeutic solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance</td>
<td>Remove sodium from nutritional sources and medications</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Adjust the dose</td>
</tr>
<tr>
<td>Reduced oral bioavailability</td>
<td>Use parental therapy, switch agents</td>
</tr>
<tr>
<td>Reduced renal blood flow (Nsaids, ACEI etc)</td>
<td>D/c the offending agent, Inc. volume, or add vasopressors</td>
</tr>
<tr>
<td>Postdiuretic salt retention</td>
<td>frequent dosing, Cont IV infusion</td>
</tr>
<tr>
<td>Hypertrophy of DCT</td>
<td>Combo diuretic therapy (metolazone(2.5-5mg), thiazides)</td>
</tr>
</tbody>
</table>
Diuretic Monitoring

- Weight loss or gain (1-2 lbs/day; faster initially?)
  - Peripheral edema, neck veins (JVD)
- Blood pressure (postural changes, dizziness)
  - Volume depletion
- Serum potassium (hypokalemia)
  - Are K+ supplements necessary? How much?
  - Role of potassium sparing diuretics (triamterene; Dyazide)
Diuretic monitoring

- Serum magnesium (hypomagnesemia): arrhythmias
- BUN and serum creatinine
  - volume depletion (pre-renal azotemia)
  - Consider effect of heart failure status
- Rash (sulfa structure), hearing loss
Vasodilators

- Afterload reduction (arterial dilation) to increase cardiac output
- Preload reduction (venous dilation) to reduce pulmonary and venous congestion
- Hydralazine (after-load) plus nitrates (pre-load)
- ACE inhibitors (mixed preload and afterload reduction)
- Angiotensin receptor antagonists
ACE Inhibitors
Stage A-Class IIa
• Antigiotensin converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: A)

Stage B-Class I
• Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI. (Level of Evidence: A)

Stage C-Class I
• Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. (Level of Evidence: A)
Mechanism of action: ACE inhibitors
(ASSUMED KNOWLEDGE)

Low renal volume/pressure

Renin release from kidney

Angiotensinogen

Angiotensin I

Angiotensin converting enzyme (ACE), kinase II

Inactive fragments

Angiotensin II

Angiotensin receptors

Peripheral vasculature

Vasoconstrict

Efferent Arterioles

Vasoconstrict

Adrenal gland

Aldosterone
Na+ retention

Kininogen → Kallikrein → Bradykinin

Airway irritant?

Vasodilate
ACEI Trials

NYHA class I

SOLVD prevention (enalapril)

Class II

SOLVD Treatment (enalapril)

Class III

V-heft II (enalapril)

Class IV

Consensus (enalapril)

NEJM 1987; 316: 1429-5

NEJM 1991; 325: 293-302

NEJM 1991; 325: 303-10
ACE Inhibitors in Heart Failure: From Asymptomatic LVD to Severe HF

SOLVD Prevention

CONSENSUS

SOLVD Treatment


# ACE Inhibitors

Drugs of choice for all HF patients

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril (Lotensin)</td>
<td>5, 10, 20, 40 mg tabs</td>
</tr>
<tr>
<td>Captopril (generic, Capoten)</td>
<td>12.5, 25, 50, 100 mg tabs</td>
</tr>
<tr>
<td>Enalapril (generic, Vasotec)</td>
<td>2.5, 5, 10, 20 mg tabs</td>
</tr>
<tr>
<td>Fosinopril (Monopril)</td>
<td>10, 20, 40 mg tabs</td>
</tr>
<tr>
<td>Lisinopril (generic, Prinivil, Zestril)</td>
<td>5, 10, 20, 40 mg tabs</td>
</tr>
<tr>
<td>Moexipril (Univasc)</td>
<td>7.5, 15 mg tabs</td>
</tr>
<tr>
<td>Perindopril (Aceon)</td>
<td>2, 4, 8 mg tabs</td>
</tr>
<tr>
<td>Quinapril (Accupril)</td>
<td>5, 10, 20, 40 mg tabs</td>
</tr>
<tr>
<td>Ramipril (Altace)</td>
<td>1.25, 2.5, 5, 10 mg tabs</td>
</tr>
<tr>
<td>Trandolapril (Mavik)</td>
<td>1, 2, 4, mg tabs</td>
</tr>
</tbody>
</table>
ACE Inhibitors: Place in therapy

Patients with systolic heart failure should be taking an ACE inhibitor for morbidity/mortality benefits.

For patients with contraindications or unable to tolerate ACE inhibitors:
  - alternative vasodilator therapy - hydralazine/nitrate combination
  - or
  - ARBs
Clinical benefits of ACEIs

• Hemodynamic improvements
• Improved exercise tolerance
• Decreased symptoms of HF
• Fewer hospital admissions
• Fewer treatment failures
• Slowed progression of disease
• Prolonged survival
ACE inhibitor side effects

- Hypotension and first dose bradycardia
- Cough 5-10% (higher in women or Asians?)
  Renal effects
  - Worse: volume depleted, RA stenosis, low BP
- Angioedema <1%. (higher is blacks?)
- Teratogenic (2nd or 3rd trimester; renal, facial)
- Hyperkalemia
- Rash and taste disturbance (high dose captopril).
Balancing effects on the kidney

Prostaglandin E, prostacyclin: dilate
NSAIDs: constrict

Angiotensin II: constrict
ACE inhibitors: dilate
Receptor antagonists: dilate

“renal preload”

Glomerulus

Filtration

“renal afterload”

Consider role of:
1. Hypertension, renal artery stenosis
2. Hypotension, volume depletion (includes diuresis): “pre-renal”
3. Heart failure (“pre-renal” azotemia)
4. ACE inhibitors (heart failure improves vs. volume depletion)
Anigiotensin receptor blockers
Stage A-Class IIa

- Antigiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: C)

Stage B-Class I

- An ARB should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF. (Level of Evidence: B)
Background

• Despite full standard therapy, patients with CHF have a poor prognosis
• ACE inhibitors do not completely inhibit the RAAS
• Angiotensin II can be produced by alternative pathways
• ARBs may offer additional clinical benefits in HF patients who are already on ACEIs as well as an alternative for ACE intolerant patients
Renin-Angiotensin Cascade

**Angiotensinogen**

- **Renin**
  - Vasoconstriction
  - Cell growth
  - Na/H₂O retention
  - Sympathetic activation

- **Angiotensin I**
  - Non-renin (eg tPA)
  - Non-ACE (eg chymase)

- **Angiotensin II**
  - AT₁
    - Vasoconstriction
    - Cell growth
    - Na/H₂O retention
    - Sympathetic activation
  - AT₂
    - Vasodilation
    - Antiproliferation (kinins)

- **ACE**

- **Bradykinin**
  - B₂, NO
  - Cough
  - Vasodilation
  - ↓ Platelet agg
  - ↓ Ischemia
  - + inotropic
Mechanism of action: Angiotensin Receptor Blockers (ASSUMED KNOWLEDGE)

Low renal volume/pressure → Renin release from kidney

Angiotensinogen → Angiotensin I → Angiotensin converting enzyme (ACE), kinase II → Angiotensin II

ARB₁ blocker

Kininogen → Kallikrein → Bradykinin → Inactive fragments

Vasodilate

Airway irritant?

**AT₂ Receptor Stimulation**
- vasodilation
- stimulation of NO production?
- regression of hypertrophy
- apoptosis

**AT₁ Receptor Stimulation**
- vasoconstriction
- aldosterone & vasopressin secretion
- sodium reabsorption
- catecholamine release
- LV remodeling, growth stimulation
Outcome trials with ARBs in HF

• ELITE II (2000)  
  Class II-IV, LVEF <40%, comparing losartan to captopril
• Val-HeFT (2001)  
  Class II-IV, LVEF <40%, Valsartan vs placebo
• CHARM (2003)
CHARM Program

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

<table>
<thead>
<tr>
<th>CHARM Alternative</th>
<th>CHARM Added</th>
<th>CHARM Preserved</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2,028 LVEF ≤ 40% ACE inhibitor intolerant</td>
<td>n = 2,548 LVEF ≤ 40% ACE inhibitor treated</td>
<td>n = 3,025 LVEF &gt; 40% ACE inhibitor treated/not treated</td>
</tr>
</tbody>
</table>
CHARM

- For each of the three component Trials
  **Primary outcome** was the effect of candesartan on the combined end point of cardiovascular mortality and heart failure hospitalization

**Secondary outcomes included:** CV death, admission to hospital for HF, or non-fatal MI, or non-fatal stroke, coronary revascularization, death, development of new diabetes
**CHARM – Alternative:**
Primary outcome CV Death or CHF Hospitalization

**CHARM – Added:**
Primary Outcome CV Death or CHF Hospitalization

**CHARM – Preserved:** Primary Outcome CV Death or CHF Hospitalization

**Cardiovascular and non-cardiovascular death**

[Graphs and tables showing data and hazard ratios for each outcome]
# Angiotensin Receptor Blockers (ARBs)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Strength/ HTN dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candesartan</strong> (Atacand)</td>
<td>4, 8, 16, 32 mg tabs; 8 mg QD-16 mg BID</td>
</tr>
<tr>
<td>HF trials. Approved 5/05</td>
<td></td>
</tr>
<tr>
<td>Eprosartan (Teveten)</td>
<td>400, 600 mg tabs; 400–800 mg QD/BID</td>
</tr>
<tr>
<td>1 HF trial</td>
<td></td>
</tr>
<tr>
<td>Irbesartan (Avapro)</td>
<td>75, 150, 300 mg tabs; 150-300 mg QD</td>
</tr>
<tr>
<td>1 HF trial</td>
<td></td>
</tr>
<tr>
<td>Losartan (Cozaar)</td>
<td>25, 50 mg tabs; 25-100 mg QD/BID</td>
</tr>
<tr>
<td>9 HF trials</td>
<td></td>
</tr>
<tr>
<td>Olmesartan (Benicar)</td>
<td>5, 20, 40 mg tabs; 5-40 mg QD</td>
</tr>
<tr>
<td>Telmisartan (Micardis)</td>
<td>20, 40, 80 mg tabs; 20-80 mg QD</td>
</tr>
<tr>
<td>Valsartan (Diovan)</td>
<td>40, 80, 160, 320 mg tabs; HF: 40 BID-160 BID</td>
</tr>
<tr>
<td>3 HF trials (Approved 9/02)</td>
<td></td>
</tr>
</tbody>
</table>
Practice implications

• ARB is a good alternative in ACE intolerant patients

• Adverse effects are likely to be more in routine clinical practice therefore close monitoring is required

• Use drugs that have shown to reduce clinical end points in large trials and use doses that have shown to be effective and safe

• Not a class effect
Aldosterone antagonists
Aldosterone antagonists
ACC/AHA 2005

• Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/l. *(Level of Evidence: B)*
Aldosterone Inhibitors
Spironolactone

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

- **Retention Na⁺**
- **Retention H₂O**
- **Excretion K⁺**
- **Excretion Mg²⁺**

→ Edema

→ Arrhythmias

• Collagen deposition
- myocardium
- vessels

ALDOSTERONE
Aldosterone antagonists

- Spironolactone (Aldactone)
- Eplerenone (Inspra)

- Likely mechanism of action
  - neurohormonal inhibition; slowed remodeling (esp fibrosis) of LV and thus slowed progression of heart failure
# Aldosterone Antagonist Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>LVEF</th>
<th>Beta-blockers</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>Severe HF</td>
<td>26%</td>
<td>11%</td>
<td>Initial dose 12.5mg QD</td>
</tr>
<tr>
<td>Spironolactone (30%RR)</td>
<td></td>
<td></td>
<td></td>
<td>Mean dose 27mg QD</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>MI with evidence of HF</td>
<td>33%</td>
<td>75%</td>
<td>Initial 25-mg QD</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>(15%)</td>
<td></td>
<td>Beta-blockers</td>
<td>Mean dose 43mg/d</td>
</tr>
</tbody>
</table>

Sources:
- NEJM1999;341:709-717
- NEJM2003;348:1309-1321
Hyperkalemia with Spironolactone (NEJM Aug 5, 2004)

• 5 X increase in # of prescriptions and 3X incidence of hyperkalemia since RALES
  – 1/3 had renal insufficiency or diabetes
  – > 1/3 also receiving potassium supplements
  – More use of beta blockers that also can raise K+
  – Many patients older than RALES subjects
  – Many did not have late stage HF

• 3 X increase in hyperkalemia associated deaths, but overall decrease in hospitalization and death rates for HF.
Caution – with Aldosterone Antagonists

• Spironolactone/Eplerenone are “easy” drugs to prescribe for HF!!
  – Once a day and single dose (25mg/d) – no titration

Caution:
• Significant risk of hyperkalaemia (> 5%)
  – Needs close monitoring

• 10% risk of gynaecomastia (vs <1% with eplerenone)
Hydralazine/ ISDN
Stage C-Class IIa

- The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. (Level of Evidence: A)

Stage C-Class IIb

- A combination of hydralazine and nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. (Level of Evidence: C)
Mechanism of Drug Effects

- **Isosorbide dinitrate**
  - Nitric oxide donor
  - Large and small artery dilator
  - Venous dilator
- **Hydralazine**
  - Antioxidant (Inhibits destruction of NO)
  - Arteriolar dilator
- **BiDil**
  - Fixed-dose I/H
  - Nitric oxide enhancer
Hydralazine/Isosorbide

- Mortality: less than with placebo, but greater than enalapril
- Additive to ACEIs?
- More effective in Blacks than ACEI? (BiDil)
- Inconvenient dosing: Hydralazine 25-50 mg QID, Isordil 10-40 mg TID
A-HEFT trial

- 1050 AA patients with advanced HF

ISDN+hydralazine  
N=518

Placebo(N=532)

Primary end point
Weighted composite of all cause mortality, first hospitalization for HF, and change in QOL at a mean follow up of 10 months

NEJM 2004;351:2049-57
A-HeFT: Conclusions

• Fixed-dose I/H benefits African American HF patients treated with neurohormonal blockers:
  – Increases survival by 43%
  – Decreases first hospitalization for HF by 33%
  – Improves QOL

• Nitric oxide enhancing therapy is a novel and highly effective heart failure treatment
Adverse effects

• Side effects
  – Hydralazine: hypotension, headache, tachycardia (less in HF), lupus like syndrome (+ANA)
  – Nitrates: Hypotension, headache, flushing, ?tolerance

• Not recommended unless unable to tolerate ACEI.
Beta-Blockers
Beta -blockers

- Stage B-Class I
- Beta blockers and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF. (level of Evidence: A)
- Beta –blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms

- Stage C-Class 1
- Beta blockers are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF unless contraindicated
Beta blockers in heart failure?

- Sympathetic nervous system activation (norepinephrine)
  - Peripheral vasoconstriction
    - Pro: maintain BP if CO low; improve ventricular filling
    - Con: ↑ afterload, ↑ ventricular volume, Na+ retention via ↓ renal blood flow
  - ↑ HR, ↑ contractility
    - Pro: initial help to maintain CO
    - Con: ventricle wall hypertrophy/fibrosis, ischemia, arrhythmias
  - Hyperkalemia: arrhythmias
  - Oxidative stress, programmed myocardial cell death and apoptosis
  - Normal ratio of β₁:β₂ receptors in heart is 80:20
    - Balanced shifted to 60:40 in failing myocardium due to down-regulation of β₁ subtype. (Negative feedback response to activation)
    - α₁ subtype up-regulated in failing heart → cell growth and positive inotropism
Beta- blocker trials

MERIT-HF (Lancet 1999)

CIBIS-II (Lancet 1999)

COPERNICUS (NEJM 2001)

COMET (Lancet 2003)
COMET Trial

• >3000 pts with NYHA II-IV HF
  – Carvedilol 25 mg BID
  – Metoprolol IR 50 mg BID
• CV deaths = 29% carvedilol, 35% metoprolol after mean of 58 months follow up.
• Hypotension = 14% carvedilol, 11% metoprolol
• Controversy over dosage form and dose of carvedilol but…
  – Similar reduction in HR with both drugs. 13.3 BPM carvedilol vs 11.7 BPM metoprolol
Effect of Beta Blockade on Outcome in Patients With HF and Post-MI LVD

Therapeutic options

- Selective beta-1 receptor blockers
  - Metoprolol tartrate immediate release (Lopressor, generic)
  - Metoprolol succinate extended release (Toprol XL)
  - Bisoprolol (Zebeta)

- Combined alpha-1, beta-1, beta-2 blocker
  - Carvedilol (Coreg). May also have antioxidant properties
Metoprolol bioavailability

• Immediate release (tartrate):
  – 50% bioavailability due to large first pass effect

• Extended release (succinate)
  – SR release beads embedded within solid tablet
    • OK to cut in half. Beads remain intact (do not chew or crush)
  – ~20 hr release: less hypotensive effect
  – 35% bioavailability: slower absorption = more first pass effect and less enzyme saturation

• Despite absorption differences, doses are similar. Titrate to response.
• Primary metabolism = O-hydroxylation, O-demethylation, N-dealkylation
• Secondary metabolism via P450-2D6.
  – 10% slow metabolizers
  – Possible drug interactions with known inhibitors (fluoxetine, paroxetine, propafenone, quinidine)
Carvedilol metabolism/drug inxs

- Take with food to slow absorption rate and hypotensive responses.
- Metabolized by CYP 2D6
- Rifampin and cimetidine induced 2D6 lowers carvedilol levels
  - Effects of other 2D6 drugs unstudied: fluoxetine, paroxetine, propafenone, quinidine
- Carvedilol reported to increase digoxin serum levels 15% by unknown mechanism
Choice of beta agonist

- Trend toward greater improvement in ejection fraction with carvedilol than metoprolol
- More hypotension and dizziness with carvedilol (rapid absorption and alpha blockade)
- Cost of carvedilol higher
- Essentially equivalent. Use metoprolol if hypotensive and carvedilol in hypertensive?
Clinical Benefit of beta-blockers

- Hemodynamic improvements (increases in EF)
- Improvements in exercise tolerance
- Decreased hospitalizations
- Decreased need for heart transplantation
- Decreased mortality (approximately 34% in placebo-controlled trials)
Beta-blockers

- Initiation of beta-blockers
- Role of beta-blockers in HF exacerbations
- Rationale for switching between beta-blockers
Beta-blocker dosing principles

• Start with low doses
  – 10-20% with initial worsening of symptoms (dizzy, fatigue, lightheadedness, weight gain, hypotension)
• Titrate slowly over several weeks (double q 2 weeks)
  – may take 2-3 months for full benefit
• Originally approved for NYHA class II and III symptoms
• Recently approved for Class IV sxs
• Avoid rapid discontinuation: risk of exacerbation
<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Goal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (Coreg)</td>
<td>3.125 mg BID (3.125, 6.25, 12.5, 25 mg tabs)</td>
<td>25 mg BID (50 mg BID if wt &gt; 85 kg) (with food)</td>
</tr>
<tr>
<td>Metoprolol rapid release</td>
<td>Not recommended (50, 100 mg tablets)</td>
<td>25-500 mg QID; 50-100 mg BID</td>
</tr>
<tr>
<td>Metoprolol CR (Toprol XL)</td>
<td>12.5-25 mg QD (25, 50, 100, 200 mg tabs)</td>
<td>150-200 mg QD; 100 mg BID</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg QD (smallest tab = 5 mg)</td>
<td>5-10 mg QD</td>
</tr>
</tbody>
</table>
Keys to successful use of beta-blockers in heart failure:

• Patient should be stable before initiation
• Therapy must be initiated with very low doses
• Titrate slowly (double dose every 2 weeks) upward to target dose
• Monitor closely for worsening HF sx, other adverse effects
Contraindications

• Cardiogenic shock
• Symptomatic Bradycardia
• 2\textsuperscript{nd}, 3\textsuperscript{rd} degree heart block without pacemaker
• Severe reactive airway disease
Side effect monitoring

• Common during first 24-48 hours after each dosing change
• Fatigue, weakness, lassitude
• Fluid retention: daily weight monitoring and observation for edema
• Bradycardia
  – Daily BP and HR monitoring
  – Continue if asymptomatic
  – Lower dose if dizzy, lightheaded, heart block
  – More with carvedilol? More rapid absorption
• Shortness of breath: volume overload vs COPD
Digoxin
Stage B-Class III
• Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit. (Level of Evidence: C)

Stage C-Class IIa
• Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. (Level of Evidence: B)
Digoxin

• Historical drug of choice
  – Based on inotropic theories, EF measures, symptom relief

• Indicated if concurrent atrial fibrillation
  – controversy over use in normal rhythm (SE risk vs. benefit)

• RADIANCE and PROVED
  – worsening symptoms if digoxin d/c’d

• Digitalis Intervention Group (DIG)
  – Fewer hospitalizations, increased QOL
  – No reduction in total mortality
Digoxin

• Exact MOA unclear; probably not due to positive inotropic effect
• Likely benefits from neurohormonal inhibition
  – decreased sympathetic outflow
  – improved baroreceptor function and increased vagal tone
• Target Cp: 0.5-1.0 ng/ml
The DIG Trial

- 6,800 patients
- EF <= 45%
- Digoxin vs placebo
- All other CHF therapies OK
- No survival benefit at 4 yrs

NEJM 1997;336:525-33
The DIG Trial, II

- Digoxin was beneficial in reducing the combined endpoint of hospitalization or death from CHF
- 8 point absolute endpoint reduction
- 18% relative risk reduction
- Thus, rational to use digoxin for LV dysfunction CHF, to reduce symptomatic progression

NEJM 1997;336:525-33
Clinical benefits associated with digoxin therapy

- Improvement in symptoms
- Improved exercise tolerance
- Improved quality of life
- Decreased number of hospitalizations
- THERE IS NO SURVIVAL BENEFIT
Digoxin

- Loading dose: Only if need rapid response
  - 0.5-1 mg IV/PO over 24 hr (0.01-0.02 mg/kg)
- Maintenance dose: 0.125-0.25 mg/day
Digoxin Toxicity /side effects

• **CNS:** H/A, dizziness, halos, changes in yellow/green color perception
• **GI:** anorexia, N/V, diarrhea, constipation
• **Cardiac:** Bradycardia (AV block), HR < 50, ↑ PR interval
  – PVCs, other arrhythmias (myocardial irritability)
Digoxin

- Risk factors for digoxin toxicity:
  - decreased renal function
  - increased dose/overcompliance
  - hypokalemia
  - Interacting drugs
Management of digoxin Toxicity

- Withhold drug 1-2 half-lives
- Potassium replacement (10-40 mEq/hr) unless ↑ serum K⁺
- Magnesium replacement unless ↑ serum Mg⁺
- Atropine 0.5-1 mg for bradycardia
- Lidocaine or phenytoin for V. ectopy
- Severe: Digoxin specific antibody fragments
  - Digoxin immune Fab (Digibind, DigiFab)
  - Antibody binds free digoxin in serum making it unavailable for receptor binding in heart and other tissues.
  - Digoxin-antibody complex excreted in urine
Digoxin interactions

- **Increased serum concentration**
  - Amiodarone (reduced clearance by ?mechanism, also mild negative inotropic effect)
  - Carvedilol. Mechanism ?
  - Erythromycin (altered GI metabolism, p-glycoprotein inhibition?)
  - Itraconazole (reduced clearance by ?mechanism)
  - Omeprazole increased bioavailability by unknown mechanism

- **Decreased serum concentration**
  - Altered absorption: antacids, colestipol, laxatives