HST-151   1

HST150 – Principles of Pharmacology
Spring 2003

Vasoactive Medications II:
Heart Failure

Heart Failure (HF): The Scope of the Problem

- HF afflicts 4.8 million adults in the US (1.5-2.0% of entire US population)
- 400,000-700,00 new HF cases/year in US
- 250,000 deaths/year in US due to HF
- Mortality: mild symptoms 5-10%/year; severe symptoms 30-40%/year; overall 50% 5 year survival
- Cost: $20-40 billion/year (75% of this for hospitalizations)

Definition of HF

- Despite the prevalence of HF, there remains as yet no consensus definition
- *Braunwald Definition*: A *pathophysiologic state* in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues or to do so only at higher than normal filling pressures.

Etiology of HF

- HF may be caused by a predominant problem of cardiac ejection (systolic heart failure) or cardiac filling (diastolic heart failure)

- The cardiomyopathies have been historically divided into dilated, restrictive and hypertrophic subtypes. Dilated cardiomyopathies evidence predominant systolic heart failure, restrictive and hypertrophic cardiomyopathies predominant diastolic heart failure (at least early in their respective courses)

Common Causes of Systolic HF

- Coronary artery disease (2/3 of cases in US)

- Hypertension
- Alcohol
- "Idiopathic" (30-50% familial/genetic)
- Valvular disease (aortic and mitral regurgitation, late aortic stenosis)
- Toxic (chemotherapy)
- Myocarditis (viral, hypersensitivity)

Common Causes of Diastolic HF

- Hypertension
- Ischemia
- Idiopathic restrictive cardiomyopathy
- Aortic stenosis
- Infiltrative myocardial disorders (amyloidosis, sarcoidosis)
- Pericardial disease (although not strictly a disease of myocardium, pericardial diseases may mimic clinical and hemodynamic features of restrictive cardiomyopathy
- Radiation or chemotherapy induced fibrosis

Mechanism of HF Symptoms

- Two main symptom classes: congestive vs. low-output
- Determinants of symptoms are both cardiac and non-cardiac in origin:
  Cardiac
    - Left ventricular systolic function (cardiac output)
    - Left ventricular diastolic function (pulmonary congestion)
    - Valvular disease (esp. mitral or tricuspid regurgitation)
    - Arrhythmias (paroxysmal or sustained)
  Non-cardiac
    - Sodium and water retention (congestion due to overload)
    - Peripheral vascular tone (vasoconstriction)
    - Skeletal muscle fiber type, perfusion and function
    - Pulmonary mechanics and ventilatory muscle function
    - Reflex neurohormonal activity

Pathophysiologic Mechanisms of HF

Initiating mechanisms: myocardial injury, depression of contractile function or myocardial "overload" (pressure, volume) -> see appendix

Mechanism of Progression: *adverse ventricular remodeling and neurohormonal activation*

- Remodeling defined: an alteration in ventricular mass, dimension, configuration without a corresponding change in number of ventricular myocytes
- Remodeling occurs in response to many of the same factors which initiate HF. The most important factors include 1) chronic pressure/volume overload (via activation of myocardial paracrine and autocrine growth and trophic pathways, ventricular hypertrophy and dilation ensue) and 2) neurohormonal activation (e.g., epinephrine, norepinephrine, angiotensin II, aldosterone).
- Neurohormonal activation results in peripheral vasoconstriction and sodium retention and important direct hormonal myocardial effects. Both peripheral neurohormonal activation (kidney, vascular endothelium) and intrinsic myocardial neurohormonal activation (myocardial RAS system and cytokine production) are important.
- **The current chronic oral pharmacological therapies which reduce mortality in systolic HF are all neurohormonal antagonists (ACEI, β-blockers, spironolactone) which have effects on blunting both the peripheral and myocardial neurohormonal activation which characterizes HF.**
- **The primary current therapeutic target in chronic systolic HF is the prevention of progressive adverse ventricular remodeling with neurohormonal antagonists**.

Non-pharmacologic General Therapeutic Measures for HF

General counseling

Prognosis

Activity recommendations

Dietary recommendations

Medications

Importance of Compliance with the Treatment/Care Plan

Pharmacological Therapy of HF: Goals and Principles

Goals of Pharmacological Therapy
- Relieve symptoms and signs of congestion
- Relieve symptoms and signs of inadequate perfusion
- Inhibit ventricular remodeling
- Improve quality of life
- Prolong survival

Principles of Pharmacological Therapy
- "Let's take the congestion out of congestive heart failure…"-Lynne Warner Stevenson

A stable congestion-free state should always be the "background" upon whichneurohormonal antagonists are titrated/adjusted. This is achieved by appropriate dosage of maintenance diuretics, a flexible sliding-scale diuretic regimen based upon daily weights, dietary restriction of sodium in all patients (2,000 mg/d) and dietary restriction of total daily fluid intake in most patients (2-3 L/d).

- Anti-remodeling by neurohormonal antagonism (ACEI, β-blockers, spironolactone) should be advanced at least to doses achieved in clinical mortality trials whenever possible

Specific Pharmacological Agents

Diuretics

- Diuretics have never been studied in clinical trials in heart failure although they obviously play a key role in acute symptom relief and chronic management via "clamping preload".
- In general, the goal in treating chronic HF should be to <u>titrate to the minimum effective dose</u> of diuretic required to control symptoms and volume.
- Since patients with heart failure often exhibit diuretic "resistance", they often require high or escalating doses of diuretics as the severity of HF progresses.
- Excessive use of diuretics however may be harmful in HF as it promotes volume depletion and resultant reflex activation of the sympathetic nervous system and renin-angiotensin system (i.e., excessive diuretic use acts as a "neurohormonal agonist".
- Since diuretic therapy usually results in prompt and gratifying symptom relief in episodes of acute HF decompensation, patients (and sometimes their physicians) sometimes over-rely on the short-term benefits of diuretic therapy and do not focus instead on the longer-term benefits of neurohormonal antagonists.
- In general, patients with mild volume overload and preserved creatinine clearances may be treated with a thiazide diuretic.
- Patients with more severe volume overload, estimated creatinine clearances less than 30 mL/min or persistent edema despite a thiazide require a loop diuretic, usually furosemide.
- Proper diuretic dosing depends on size, age, renal function, ACEI dosing, compliance with dietary sodium restriction and the amount of edema present.

- There are not standard target doses of diuretics in HF. The dose of furosemide in patients with truly refractory HF and diuretic resistance may have to be increased to up to 240 mg or more a day in divided doses. Most cardiologists would add low-dose metolazone (a very potent thiazide-like diuretic which acts by a different mechanism) once the dose of furosemide exceeds 120 mg bid (see below). All dosing should be predicated upon daily weight determinations, signs of volume status (JVP, rales, hepatomegaly, edema) and maintenance of acceptable electrolyte concentrations (particularly serum potassium and magnesium).
- Once a day furosemide (or other loop diuretic) dosing is preferred until the dose of furosemide exceeds 80-120 mg once daily and fails to effect an adequate diuresis-then twice daily dosing or furosemide 80-120 mg bid may be effective.
- Furosemide doses > 160-240 mg/day may require additional measures/agents:
  - Oral metolazone 2.5-10 mg/day: this diuretic is extremely potent and may result in hypotension and hypokalemia. In particular, the combination of the loop diuretic and metolazone can be extremely kaliuretic and patients require supplemental potassium and electrolyte monitoring frequently (e.g., every 3 days until stable).
  - Intravenous loop diuretics on a periodic basis
  - Intravenous thiazide diuretics such as hydrodiuril on a periodic basis
  - Spironolactone 25-50 mg day: this agent may promote hyperkalemia, especially in diabetics with Type IV RTA and maintenance potassium supplements often require adjustment – as discussed below, spironolactone should be provided to all suitable patients with advanced (NYHA III-IV) symptoms based on results from the **RALES** trial
  - "Renal dose" dopamine (for hospitalized patients)
  - Intravenous inotropes such as dobutamine (for extremely ill hospitalized patients)
  - Dialysis

Angiotensin Converting Enzyme Inhibitors (ACEI)

Mechanism

- ACEI inhibit 1) angiotensin converting enzyme which converts angiotensin I to angiotensin II thereby inhibiting the production of angiotensin II and 2) various kininase enzymes which breakdown bradykinin and other kinins thereby increasing the half-life and effects of bradykinin and other vasodilatory kinins
- Both peripheral and myocardial RAS systems are inhibited
- Although ACEI differ with respect to pharmacokinetics and tissue-binding properties, there are as yet no clear data that any individual ACEI is more effective than any other ACEI in the therapy of chronic systolic heart failure. To date, it thus appears that the benefit of ACEI therapy in HF may be a class effect (i.e., any ACEI inhibitor dosed appropriately may be effective).

Clinical Trials in Chronic Systolic Heart Failure

- From these studies, ACEI in chronic systolic HF have the following effects:
  - Reduction in mortality in symptomatic HF patients (NYHA II-IV): this reduction in approximately 16% in NYHA II-III (*SOLVD Treatment*) and 27% in NYHA IV (*CONSENSUS I*)
  - Reduction in symptoms in patients with symptomatic heart failure (NYHA II-IV)
  - Reduction in hospitalizations in symptomatic patients (NYHA II-IV)
  - Delay in onset of symptoms in asymptomatic LV dysfunction (*SOLVD Prevention*)
  - Inhibition of LV remodeling in both symptomatic (*SOLVD Treatment)* and asymptomatic (*SOLVD Prevention*) CHF patients
  - No conclusive data yet for mortality reduction in asymptomatic LV dysfunction (i.e., NYHA I "HF")
  - Reduction in maintenance diuretic requirements
  - Improvement in exercise tolerance (quite modest benefit)
  - Improvement in quality of life
  - Improvement in ejection fraction (quite modest effect)
  - Beneficial effects observed in mild-severe heart failure regardless of etiology
- Excluded from the ACEI trials were patients with preserved ejection fraction (LVEF > 40%), low blood pressure (< 90 mmHg), severe impairment of renal function
- Dosage of ACEI appears to be important: *ATLAS* trial
- Based on the results of the *ATLAS* trial, it is recommended that every effort be made to increase the dose of ACEI to the target doses used in

clinical trials (e.g., captopril 50 mg tid, enalapril 20 mg qd, lisinopril 20 mg qd)
- Current agents FDA-approved for chronic CHF therapy: captopril, enalapril, lisinopril, quinapril, fosinopril

Clinical Trials in Post-Myocardial Infarction Patients

- In an overview of these trials, ACEI use early post-MI resulted in a 7% reduction in all-cause mortality (p=0.004) at 5 weeks. ACEI started early in acute MI prevents approximately about 6 deaths per 1000 treated overall and 15 deaths due to heart failure per 1000 in the 1st 4 weeks. In patients with anterior MI, ACEI prevents approximately 16 deaths per 1000.

Selection of Patients with chronic systolic CHF for ACEI
Indication
- LVEF ≤ 40% with or without symptoms of HF

Absolute contra-indications:
- Angioedema
- Anuric renal failure
- Shock

Relative contra-indications
- SBP ≤ 80 mmHg
- Cr >3.0 mg/dL (must exclude bilateral renal artery stenosis)
- Bilateral renal artery stenosis (use with great caution)
- Serum potassium > 5.5 mmol/L (prior to control)

Initiation/titration
- Start low dose (captopril 6.25 mg tid, enalapril 2.5 mg qd, lisinopril 2.5 mg qd)
- Double dose every 3-7 days as tolerated
- Check Cr, K q 1-2 weeks after up-titration (esp. in setting of hypotension, hyponatremia, diabetes,
   Cr > 2.0, K > 4.5)
- Appropriate adjustments: K repletion, K-sparing diuretics
- Targets: captopril 150 mg qd, enalapril 20 mg qd, lisinopril 20 mg qd
- Clinical response may be delayed 1-2 months
- Don't withdraw ACEI abruptly unless necessary (usually for hypotension, rising BUN/CR): may lead to clinical deterioration
- Avoid chronic NSAIDs

Risks of Therapy
Hypotension
- Blood pressure declines in nearly all patients on ACEI

- Problematic: orthostasis, Cr > 1.0 mmol/L, blurry vision, near-syncope/syncope
- Most common in hyponatremic patients (Na < 130 mmol/L) or after/during rapid diuresis
- Symptomatic hypotension may not recur with repeated administration

Elevation of serum creatinine
- Most common in hyponatremic or NYHA class IV patients
- Increase in Cr > 0.5 mg/dL in 15-30% with severe HF, 5-10% with mild-moderate HF
- Higher risk: bilateral renal artery stenosis, chronic NSAID use
- Usually improves after decrease in diuretic dose

Hyperkalemia
- Especially with elevated creatinine, potassium supplements, diabetes mellitus

Cough
- Occurs in 5-15% of patients
- Characteristics: non-productive, non-effort related, chronic; onset usually after weeks/months of therapy; resolves in 1-2 weeks after discontinuation of ACEI; recurs within days of rechallenge with ACEI.
- Must exclude elevation of PCWP prior to discontinuation of ACEI

Angioedema
- < 1% of treated patients but may be life-threatening

Hydralazine-Isosorbide Dinitrate Combination

Mechanism of action
- Hydralazine is a direct arteriolar smooth muscle vasodilator. It may decrease the development of nitrate tolerance when used in combination with chronic nitrates.
- Isosorbide dinitrate is an organic nitrate that is biotransformed to nitric oxide and is primarily a venodilator

Recommendation
- Given the absence of significant mortality benefit in chronic CHF, the hydralazine-nitrate combination is not FDA approved for the treatment of chronic systolic CHF
- However, the hydralazine-nitrate combination is still occasionally used in CHF patients with an absolute contraindication to ACEI or ARB (usually patients with advanced renal dysfunction) or in patients who remain significantly hypertensive despite maximal doses of combined ACEI, ARBs and β-blockers

β-blockers

Mechanism
- Inhibition of the sympathetic nervous system (vasoconstriction, sodium retention, hypertrophy, arrhythmias, apoptosis) including the effects of both myocardial norepinephrine (neurotransmitter at myocardial adrenergic nerve terminals) and circulating epinephrine

Types
- β_1 (selective): metoprolol, bisoprolol
- β_1, β_2 (non-selective): bucindolol
- β_1, β_2, α_1: carvedilol

Trials
- To date, there have been over 20 placebo-controlled trials conducted in over 10,000 patients; all trials except **COPERNICUS** have enrolled patients in NYHA II-III with LVEF < 45% receiving concurrent therapy with ACEI, diuretics, digoxin. Positive studies to date: Carvedilol, metoprolol, bisoprolol.

- <u>Excluded in trials to date</u>: normal LVEF, HR < 65 bpm, PR interval > 0.24 ms, SPB < 85 mmHg, Cr > 2.5 mg/dL

Effects
- Decrease in mortality in NYHA II-IV patients already treated with ACEI, diuretics, digoxin (approx. 30%)
- Increase in LVEF (4-7%) by 6 months
- No change in exercise tolerance
- Decrease in hospitalizations
- Decrease in symptoms
- Increase in quality of life

Role
- <u>β-blockers should be prescribed for all eligible patients without contraindication with stable class II-IV HF and LVEF $\leq$ 45%</u>

Selection of Patients
- Absolute contra-indications to initiation:
     Symptomatic bradycardia and without pacemaker
     Advanced heart block with symptoms and without pacemaker
- Relative contra-indications to initiation:
     Acutely decompensated HF (hospitalized patients)
     Significant fluid retention requiring vigorous diuresis
     Intravenous therapy for HF
     Hospitalization for HF
     Anticipated need for inotropic support in near future

Initiation/Maintenance
- Start at low dose (carvedilol 3.125 mg bid, bisoprolol 1.25 mg qd, metoprolol 12.5 mg SR qd)
- Double dose every 2-4 weeks as tolerated: slow up-titration recommended
- Monitor: hypotension, bradycardia, fluid retention, worsening HF
- In trials, 85-90% of HF patients tolerated β-blockers (? translatable to "real-time" practice)
- Target doses: carvedilol 50 mg/d, bisoprolol 10 mg/d, metoprolol 200 mg/d
- If target doses are not attainable, maintain highest tolerated dose: still beneficial in moderate dose range
- May require 2-3 months of therapy for symptomatic benefit, 6 months for improvement in LVEF
- Choice of β-blockers: await result of **COMET** trial in 2003 (carvedilol vs metoprolol in 3,000 pts.)

Risks
- Hypotension (especially prominent with carvedilol given α_1-blocking effects)-stagger dosing intervals with other vasodilators, adjust diuretics if necessary
- Fluid retention: check weights, adjust sliding scale diuretics
- Bradycardia/heart block: occurs in 5-10% during dose titration; decrease dose by 50% if HR < 50, asymptomatic 2nd or 3rd degree heart block, monitor drug interactions

Aldosterone antagonists

Mechanism
- Inhibition of aldosterone, an important hormonal modulator of ventricular remodeling

Clinical trials
- To date only one large trial of aldosterone antagonists has been completed: RALES study
- Aldosterone antagonists lacking the gynecomastia-related adverse effects of spironolactone are currently under investigation.

Selection of patients
- Based on this single study to date (RALES - which demonstrated a 30% reduction in mortality, upon "background" therapy with ACEI, diuretics and digoxin), spironolactone is recommended for patients with severe HF (NYHA III-IV); efficacy in patients with mild-moderate HF (NYHA I-II) is presently unknown.

Risks
- Hyperkalemia: particularly in diabetics, patients with Type IV renal tubular acidosis, chronic renal insufficiency

Digoxin

Mechanism
- Inhibits Na-K ATPase and thereby increases myocardial contractility to a modest extent
- More importantly, decreases CNS sympathetic outflow via vagotonic effect and therefore inhibits sympathetic stimulation to the heart-this explains the clinical observation confirmed in digoxin "withdrawal" study that cessation of digoxin may lead to symptomatic deterioration/decompensation
- Via NA-K ATPase inhibition, also decreases tubular sodium reabsorption and promotes modest natriuresis

Clinical Trials
- There have been two small prospective, multicenter, randomized, double-blind, placebo-controlled trials of digoxin withdrawl in patients with chronic systolic HF concurrently treated with ACEI, diuretics and digoxin. The PROVED and RADIANCE trials demonstrated that withdrawal of digozin led to symptomatic deterioration

- There has been one large multicenter, placebo-controlled, double-blind study of the mortality effects of digoxin in chronic HF (the only NIH-sponsored clinical mortality trial in HF to date). The study (DIG trial) showed no mortality benefit to patients with mild to moderate HF.

Selection of patients
- Based on results of the ***Dig Trial***, digoxin may decrease symptoms, improve clinical status and decrease the risk of hospitalization for HF but not reduce mortality. Since digoxin may increase risk of arrhythmias, digoxin should be used with caution in patients at high-risk of ventricular arrhythmias, especially if they are prone to hypokalemia (e.g., high doses of loop diuretics or metolazone)
- Approved by FDA for treatment of HF in 1997

Dosing
- 0.125-0.25 mg/day (dependent on renal function)
- No role for checking serum levels in absence of known/suspected toxicity

- Little relation between serum digoxin concentration and therapeutic efficacy (i.e., it is not clear that large doses of digoxin are more effective than smaller doses in the management of HF)
- Levels < 1.0 ng/ml have been associated with lower mortality in review of clinical trials

Risks
- Arrhythmias, gastrointestinal, neurologic (usually serum level > 2 ng/mL, lower with hypokalemia, hypomagnesemia, hypothyroidism)
- Drug interactions: β-blockers, spironolactone, amiodarone

Angiotensin II Receptor Blockers (ARBs)

Mechanism
- ARBs block the cell surface receptor for angiotensin II (ATII).
- There are two common ATII receptor subtypes, AT_1 and AT_2. In general, ATII binding to AT_1 results in positive inotropy, hypertrophy and proliferation in the myocardium and vasoconstriction in the periphery. In general ATII binding to AT_2 results in inhibition of proliferation and hypertrophy in the myocardium and vasodilation in the periphery result.

Clinical Trials
- There have been four trials to date of ARBs in patients with chronic systolic HF: ELITE I, RESOLVD, ELITE II, Val-HeFT. None have demonstrated to date superiority to ACEI.

Clinical Use of ARBs in chronic systolic HF
- Role unclear compared to ACEI: no persuasive evidence of equivalency/superiority of ARBs to ACEI although losartan appears to well-tolerated and nearly as effective as captopril as "monotherapy"
- No ARB is as yet FDA approved for HF
- Based on information to date, ARBs should not be used in place of ACEI in HF patients except in those truly intolerant of ACEI due to angioedema or intractable cough
- Side effects profile of ARBs (hypotension, hyperkalemia, rise in creatinine) is otherwise similar to ACEI

Calcium blockers

- Overall in studies to date, calcium channel blockers have had no consistent benefit in symptoms, exercise performance or mortality in HF
- These agents may in fact be hazardous in systolic heart failure with the exception of amlodipine: no effect on mortality or hospitalizations.

- Other calcium blockers have been associated with either no benefit or increased mortality (felopidine, mibefradil).
- Thus, calcium blockers should not be used for treatment of HF and should be avoided particularly in systolic dysfunction, even for treatment of angina or hypertension

Antiarrhythmic therapy

- Despite the fact that up to 40% of HF patients die suddenly, there is yet no compelling evidence for empiric antiarrythmic therapy in asymptomatic patients

Indications for antiarrhythmic therapy
- Sustained or hemodynamic destabilizing VT → ICD
- History of resuscitated VT/VF → ICD
- Symptomatic NSVT → individualized; usually ICD

Recurrent/sustained symptomatic atrial arrhythmias → β-blockers, sotalol, amiodarone

Recommendations
- No class I antiarrhythmic agent (quinidine, procainamide, disopyramide) should be used in HF except in immediately life-threatening arrhythmias
- Amiodarone is not currently recommended for general use to decrease mortality in patients on ACEI, β-blockers
- Amiodarone is preferred for symptomatic atrial arrhythmias despite β-blockers

Anticoagulation

- HF increases risk for thromboembolism modestly in clinically stable patients (1-2% per year)
- No controlled trials of efficacy of anticoagulation with warfarin in patients with CHF have been performed: data is retrospective and observational
- In **SOLVD** treatment cohort, retrospective analysis showed that warfarin-treated patients had a 24% reduction in mortality during follow-up (p=0.0006); given post hoc cohort analysis, significance of this is unclear
- Most recommend that anticoagulation for LVEF < 35% "...merits consideration..." after "...careful assessment of risk and benefits in individual patients...". Clearly any patient with atrial fibrillation, prior thromboembolic event or documented atrial or ventricular thrombus and CHF should be anticoagulated chronically. Many clinicians recommend anticoagulation in many if not most patients with LVEF < 20%.

Intravenous Inotropic Therapy

- Intravenous inotropes may provide short-term hemodynamic benefit, but all studies to date with positive inotropes (either oral or intravenous) have demonstrated increased mortality
- Little data on use of outpatient intravenous inotropes from randomized clinical trials: most data has been open-label, uncontrolled observational studies/reports
- In 2 placebo-controlled trials, mortality was increased with dobutamine
- Inotropes are currently labelled by FDA to discourage long-term intravenous use
- No indication for intermittent inotropes at present on an ambulatory/outpatient basis
- Indication for continuous infusion of inotropes at present is as a "bridge" to transplantation in non-dischargable patients listed for transplantation

Agents under active investigation in chronic systolic HF

Neutral endopeptidase inhibitors
Omipatrilat

Angiotensin receptor antagonists
Valsartan
Candesartan

Endothelin antagonists
Bosentan

Adenosine receptor antagonists

Vasopressin receptor antagonists

Anti-tumor necrosis factor agents

"Failed" Therapies in Chronic Systolic Heart Failure

Catecholamines: excess sudden death
Ibopamine
Xamoterol
Pirbuterol
Dobutamine

Ibopamine (oral dopamine)

Phosphodiesterase inhibitors: excess sudden death
Amrinone
Milrinone
Enoximone
Flosequinan
Vesnarinone

Direct acting vasodilators: excess mortality
Flosequinan
Epoprostenol

Alpha blockers: no better than placebo
Prazosin (***VeHFT-I***)

Alpha-2 agonists: excess mortality
Moxconidine (***MOXCON***)

Calcium channel antagonists: clinical deterioration/mortality
Verapamil (short-acting and sustained release)
Diltiazem
Nifedipine
Nicardipine
Nisoldipine
Mibefradil (***MACH-I***)
Felodipine (sustained release)
Amlodipine (neutral effect unlike other calcium blockers)

Endothelin antagonists: clinical deterioration noted early (in addition to liver toxicity)
High-dose bosentan (***REACH-1***)

"Empiric" anti-arrhythmic agents: excess mortality
Sotalol
Dofetilide

Therapy of Diastolic Heart Failure

- There have been no large trials of pharmacological therapy in heart failure with preserved LV function (diastolic heart failure)
- The major problem is abnormal ventricular compliance-this results in a lower than normal threshold for elevation of cardiac filling pressures under alterations of myocardial load

- Important agents include diuretics (reduce preload) and nitrates (reduce preload) and appropriate blood pressure control
- The rubric "...dry, slow, sinus, normotensive..." is often invoked to highlight the principles of therapy: maintainance of LV filling pressures at acceptable levels, avoidance of tachycardia (which decreases time for ventricular filling), maintenance of sinus rhythm (as atrial transport resulting from atrial systole is important in maintaining ventricular filling), control of hypertension (which raises both systolic and diastolic LV pressures)
- Any degree of myocardial ischemia clearly aggravates the already compromised compliance of the myocardium and must therefore be adequately treated
- Many anti-hyptensive agents have been shown to regress LV mass in patients with increased LV mass (ACEI, β-blockers) and thus play an important role in the most common pool of patients with diastolic heart failure, those with hypertensive heart disease
- Small trials of ACEI, ARBs and β-blockers in diastolic heart failure are ongoing at present

Lessons Learned in 25 Years of Clinical Trials with Heart Failure Drug Therapy

- Drugs that appear "theoretically" beneficial may prove harmful or lethal in clinical trials (e.g., inotropic agents with diverse mechanisms of action, Type I anti-arrhythmics)

- When a drug suspected of being efficacious turns out to be neutral or harmful in practice, it often forces a critical reappraisal of current pathophysiology and may precipitate in shift in the pathophysiologic paradigm of the disease in question (e.g., inotropes and pure vasodilators in heart failure)

- Drugs initially considered "lethal" (e.g., β-blockers in HF) may prove beneficial but re-educating physicians to use them is a long, arduous process

- Some classes of drugs appear to have "class efficacy" (e.g., perhaps ACEI in HF) and some do not (e.g., perhaps β-blockers in HF)- therefore, an individual drug of a different class can have beneficial effects even if a drug of the same class is shown not to be beneficial

- "Designer" drugs (e.g., vesnarinone) developed in animal models and tested in Phase I and II human trials may not work as designed in Phase III human trials

- Drugs may have beneficial effects not yet even suspected by the time they are tested in large mortality trials (e.g., the anti-thrombotic, anti-oxidant effects of ACEI)

- Drugs may have complex, pleotropic effects learned only after large clinical trials, especially drugs which modulate critical "multi-tasking" molecules or critical signal transduction cascades (e.g., drugs effecting norepinephrine, angiotensin II)

- Treating "secondary endpoints" successfully (e.g., eradicating PVCs on holter monitoring) may not translate into mortality benefits in real-time disease

- Drugs may have variable effects depending on the stage of the disease

- Drug therapy will ultimately prove ineffective past a threshold of mechanical inefficiency of a mechanical organ like the heart. .Non-pharmacologic strategies are then the only option

- Drugs are often "added on" in stepwise titration may complicate the dosing, titration schema and efficacy of other drugs

- Drug therapy for cardiovascular disease is quite empiric to date (including for heart failure) and not "customized" to the phenotype and genotype of the patient

- Patients may misidentify the real benefits of a drug or class of drugs when simple straightforward drugs work quickly and well (like diuretics to clear congestion); this is particularly true if the drugs do no make patients feel better on a day to day basis or cause problems like fatigue, exertional intolerance and impotence (the "Achilles heel" of β-blockers)

- Despite the billions of dollars spent in drug research and development, marketing and cajoling, many patients still just won't take them...at least not all the time...