

# **HEART FAILURE**

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**Acknowledgements :**

**American Heart Association**

**Sociedad Española de Cardiología**

## **Epidemiology**

- **More in N Europe and USA**
- **Increases with age esp in males > 75**
- **US Data**
- **5,000,000 patients**
- **6,500,000 hospital days / year**
- **300,000 deaths / year**
- **6% - 10% of people > 65 years**
- **5.4% of health care budget (38 billion)**
- **Incidence x 2 in last ten years**
- **Estimated prevalence 6 mio by 2030**

Gottdiener J et al. JACC 2000;35:1628, Haldeman GA et al. Am Heart J 1999;137:352  
Kannel WB et al. Am Heart J 1991;121:951, O'Connell JB et al. J Heart Lung Transplant  
1993;13:S107, Young J, MCNA 2004;

## **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**

*AHA / ACC HF guidelines 2001*

## **Clinical symptoms / signs secondary to abnormal ventricular function**

*ESC HF guidelines 2001*

## **“Heart Failure” vs. “Congestive Heart Failure”**

**All patients may NOT have volume overload at the time of initial or subsequent evaluation.**

**Therefore the term “heart failure” is preferred over the older term “congestive heart failure.”**

CHF is a significant cause of morbidity and mortality  
Important cause of hospitalizations among elderly

## Causes of HF

For a substantial proportion of patients, the causes of HF are:

1. Coronary artery disease
2. Hypertension
3. Dilated cardiomyopathy

And there are other causes

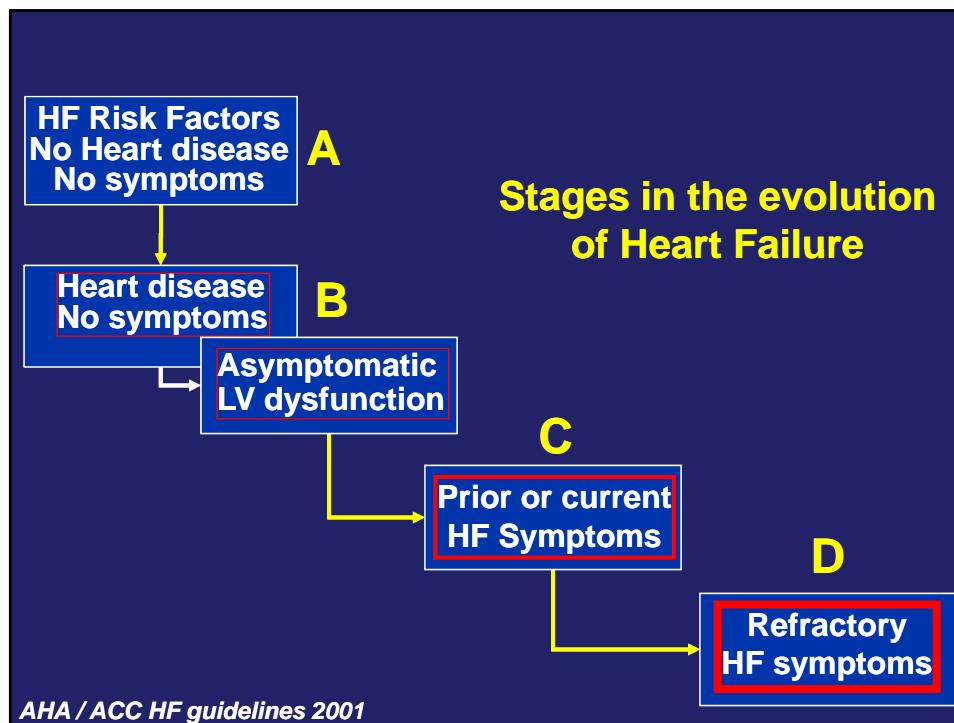
1. Hemodynamic overload
2. Ventricular filling abnormalities
3. Ventricular dyssynergy
4. Changes in cardiac rhythm

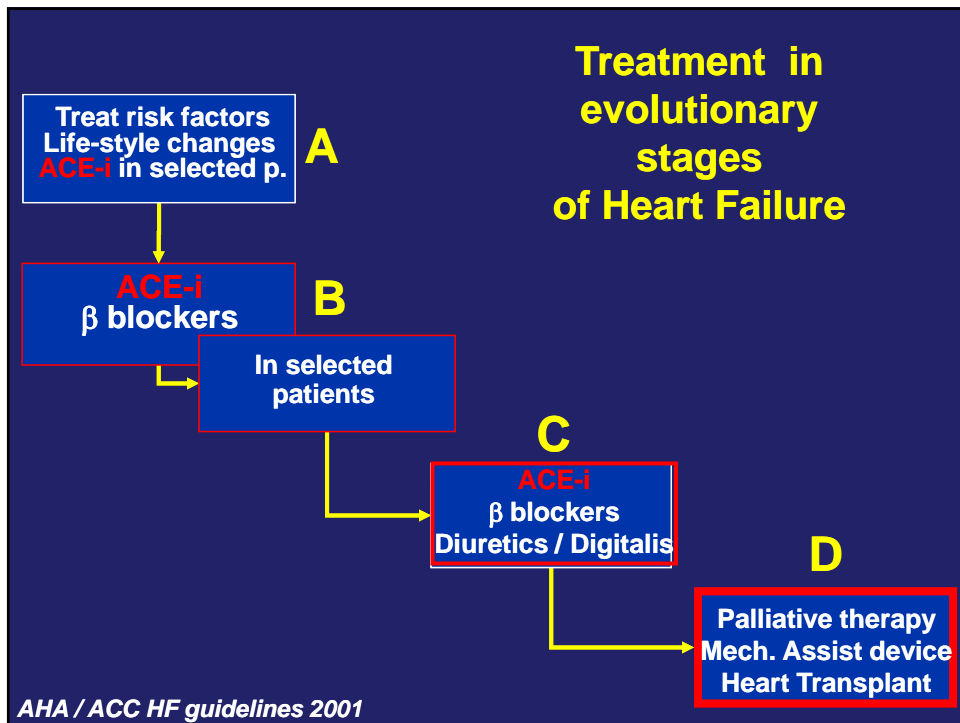
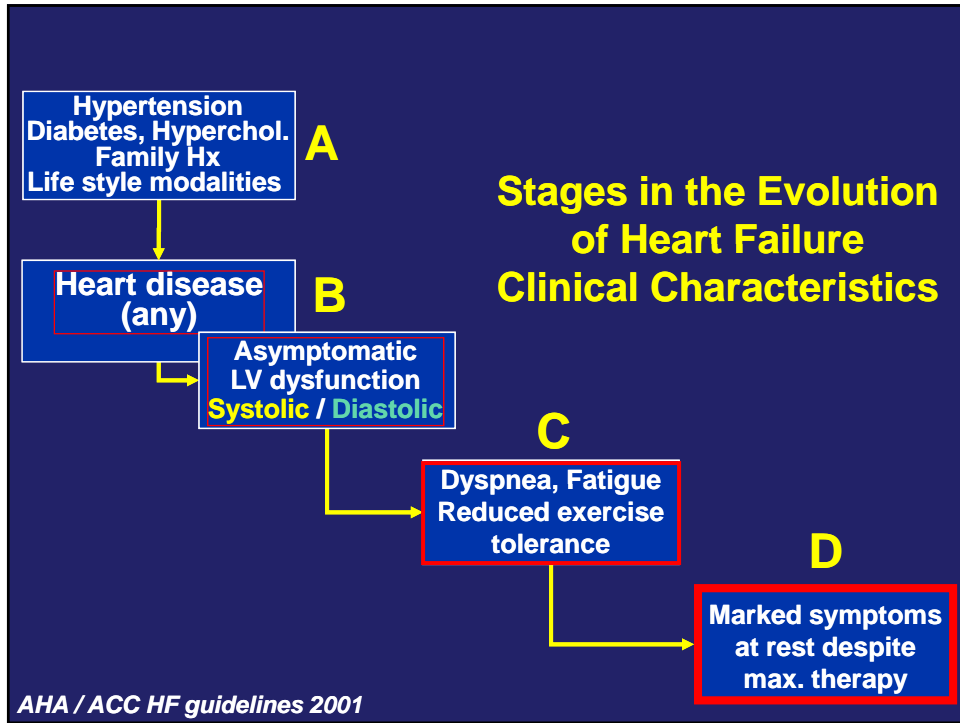
## Symptoms of CHF

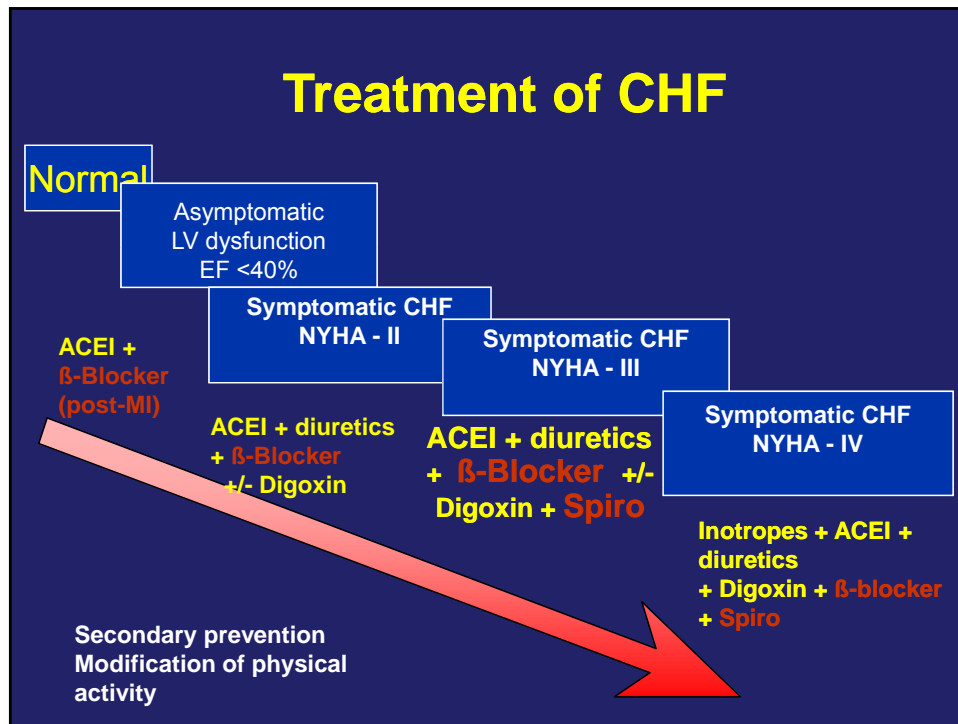
- **Due to LEFT heart failure:**  
dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), hemoptysis
- **Due to RIGHT heart failure:**  
ankle edema, abdominal pain/ or swelling/ascites, nausea/anorexia
- **Due to low cardiac output:**  
fatigue, reduced exercise tolerance, nocturia

## Signs of CHF

- Tachycardia
- Pulsus alternans
- Elevated jugular venous pressure
- Displaced apex beat
- Right ventricular heave
- Crepitations or wheeze, Rales
- Third heart sound
- Oedema
- Hepatomegaly (tender)
- Ascites
- Cachexia and muscle wasting











### *The Cardiovascular Health Study JACC 2000;35:1628*

#### Risk factors for CHF

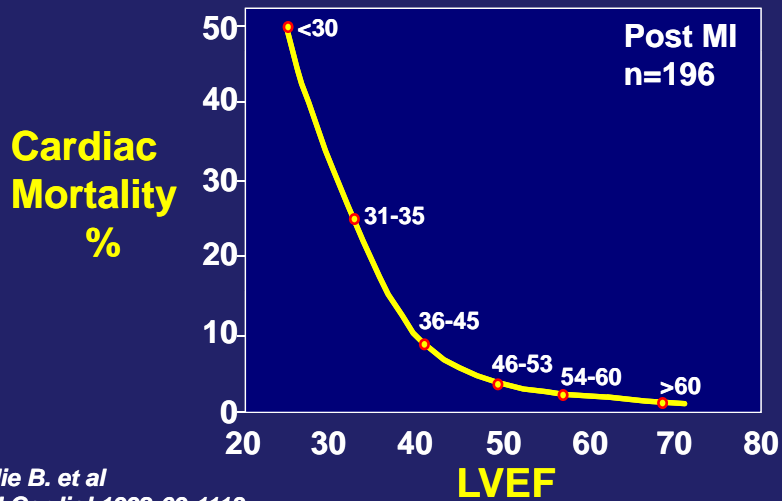
- CHD
- Systolic BP > 140 mm Hg
- Diabetes
- ECG - LVH
- Ankle swelling (Ankle-arm index > 0.9)
- ST-T segment abnormality
- Decreased LV function
- Stroke/TIA

## Initial / Ongoing Evaluation

- Identify heart disease
- Assess functional capacity (NYHA, 6 min walk, ...)
- Assess volume status: (edema, rales, jugular, hepatomegaly, body weight)
- Lab assessment: routine: electrolytes, renal funct. Repeat ECHO, RX only if significant changes in functional status
- Assess prognosis

STAGE		DISABILITY
CLASS 1 MILD		No symptoms Can perform ordinary activities without any limitations
CLASS 2 MILD		Mild symptoms - occasional swelling Somewhat limited in ability to exercise or do other strenuous activities
CLASS 3 MODERATE		Noticeable limitations in ability to exercise or participate in mildly strenuous activities Comfortable only at rest
CLASS 4 SEVERE		Unable to do any physical activity without discomfort Some HF symptoms at rest

## Prognosis



## Treatment Objectives

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



## Treatment

### Prevention

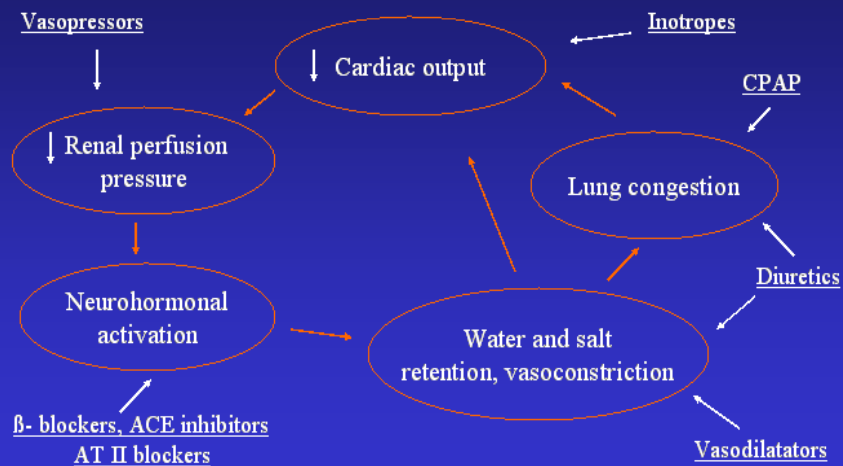
- Control of risk factors
- Life style changes
- Treat etiologic cause / aggravating factors
- Drug therapy
- Personal care
- Team work

### Recommended therapies

ACE-Inhibitors, Beta-Blockers, Diuretics and Spironolactone, Digoxin

## Drugs for CCF

### Heart Failure – vicious circle (clinical aspects)



**Natriuretic peptides** are peptide hormones synthesized by the heart, brain and other organs and released on atrial and ventricular distension, or neurohumoral stimuli, in response to heart failure

Atrial natriuretic peptide (ANP) is released by atrial myocytes on atrial distension, [angiotensin II](#) stimulation, [endothelin](#), and [sympathetic](#) stimulation (beta-adrenoceptors).

Elevated ANP is seen in hypervolemic states and congestive [heart failure](#). ANP is crucial in inducing vasodilation, promoting natriuresis, and perhaps also counteracting the pathological role from catecholamines, the RAAS and the arginine-vasopressin system.

Brain-type natriuretic peptide (BNP) is synthesized in the ventricles (it was first identified in the brain ). It is released by the same mechanisms that release ANP, constitutively by ventricular myocytes in response to stretch receptors.

BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilatation with rapid onset and offset of action by increasing levels of cGMP

Both BNP and ANP are sensitive, diagnostic markers for heart failure in patients.

Neutral endopeptidase is a circulating enzyme that degrades natriuretic peptides. Inhibition of NEP increases circulating levels of natriuretic peptide and potentiates their effects.

*NP receptor-mediated elevations in vascular smooth muscle involve cGMP which attenuates sympathetic vascular tone, either within the CNS as well as by inhibiting NorEpi release by sympathetic nerve terminals. NPs are a counter-regulatory system for the RAAS .*

**Cardiovascular and renal effects.** Natriuretic peptides (NPs) cause long-term regulation of sodium and water balance, blood volume and arterial pressure by two major pathways 1) vasodilator effects, and 2) renal effects that lead to natriuresis and diuresis.

- *NPs directly dilate veins (increase venous compliance) and thus decrease central venous pressure, ventricular preload and thereby cardiac output.*
- *NPs also dilate arteries, decrease systemic vascular resistance and systemic arterial pressure.*
- *NPs increase GFR and filtration fraction, produce natriuresis and diuresis. These effects are potassium sparing.*
- *NPs also decrease renin release, and hence circulating levels of AGII and aldosterone, causing further natriuresis and diuresis. Decreased angiotensin II decreases systemic vasodilation and systemic vascular resistance.*
- *Therefore NPs decrease blood volume, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output.*

### Cardiovascular and Renal Actions of Natriuretic Peptides

- Natriuresis
- Diuresis
- Improve glomerular filtration rate & filtration fraction
- Inhibit renin release
  - ↓ circulating angiotensin II
  - ↓ circulating aldosterone
- Systemic vasodilation
- Arterial hypotension
- Reduced venous pressure
- Reduced pulmonary capillary wedge pressure

NPs reduce systemic and pulmonary vascular resistances, which indirectly increase cardiac output and diuresis  
Effective in HF because they reduce preload and afterload  
ADR- hypotension

*A recombinant human BNP, or NESIRITIDE, is recently approved for use in the acute treatment of decompensated congestive heart failure caused by systolic dysfunction.*

*A new class of drugs that are neutral endopeptidase (NEP) inhibitors have been shown to be efficacious in animal models of heart failure. By inhibiting neutral endopeptidase, the enzyme responsible for the degradation of ANP, they elevate plasma levels of ANP. NEP inhibition is particularly effective in animal models of heart failure when the drug is combined with an **ACEI**.*

## Modulating NPs

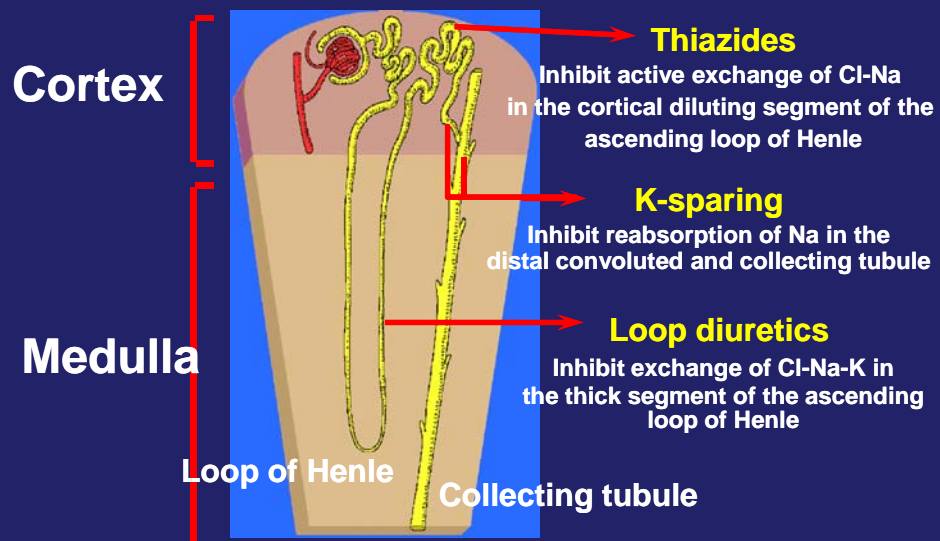
### Inhibitors of NEP

- Omapatrilat – most experience – watch for Angioedema
- Sapatrilat
- Fasidotrilat

## Pharmacologic Therapy - 4 major drugs

- Diuretics
- ACE inhibitors
- Beta Blockers
- Digitalis
- Spironolactone
- Other

### Diuretics



## Diuretics

Eliminate Na and water by acting directly on the kidney. Diuretics (loop, thiazides and potassium-sparing) produce a net loss of Na and water and decrease acute symptoms resulting from fluid retention

- **Essential to control symptoms secondary to fluid retention**
- **Prevent further progression of HF**
- **Spironolactone improves survival**

## Diuretics. When are they indicated?

- **Symptomatic HF, with fluid retention**
  - **Edema**
  - **Dyspnea**
  - **Lung Rales**
  - **Jugular distension**
  - **Hepatomegaly**
  - **Pulmonary edema (Xray)**

*AHA / ACC HF guidelines 2001*

*ESC HF guidelines 2001*

### **Loop Diuretics / Thiazides. Practical Use**

- Start with variable dose. Titrate to achieve dry weight
- Monitor serum  $K^+$  at “frequent intervals”
- Reduce dose when fluid retention is controlled
- Teach the patient when, how to change dose
- Combine to overcome “resistance”

### **Thiazides, Loop Diuretics. Adverse Effects**

- ↓  $K^+$ ,  $Mg^+$  (15 - 60%) (sudden death ???)
- ↓  $Na^+$
- Stimulation of neurohormonal activity
- Hyperuricemia (15 - 40%)
- Hypotension. Ototoxicity. Gastrointestinal. Alkalosis. Metabolic

Sharpe N. Heart failure. Martin Dunitz 2000;43, Kubo SH , et al. Am J Cardiol 1987;60:1322  
MRFIT, JAMA 1982;248:1465, Pool Wilson. Heart failure. Churchill Livinston 1997;635

## Diuretic Resistance

- Neurohormonal activation
- Rebound Na<sup>+</sup> uptake after volume loss
- Hypertrophy of distal nephron
- Reduced tubular secretion (renal failure, **NSAIDs**)
- Decreased renal perfusion (low output)
- Altered absorption of diuretic
- **Noncompliance with drugs**

*Brater NEJM 1998;339:387*  
*Kramer et al. Am J Med 1999;106:90*

## Managing Resistance to Diuretics

- Restrict Na<sup>+</sup>/H<sub>2</sub>O intake (Monitor Natremia)
- Increase dose (individual dose, frequency, i.v.)
- **Combine:** furosemide + thiazide / spiro
- Dopamine (increase cardiac output)
- Reduce dose of ACE-i

*Motwani et al Circulation 1992;86:439*



## Diuretics for CCF

Reduce symptoms of volume overload by

- decreasing extra cellular volume
- decreasing venous return
- Loop diuretics like furosemide and bumetanide are the most effective and commonly used.
- Thiazides are effective in mild cases only.

Adverse effects :

- Loop diuretics and thiazides- hypokalemia.
- Potassium sparing diuretics reduce hypokalemia due to these diuretics.

## Potassium Sparing Diuretics in CCF

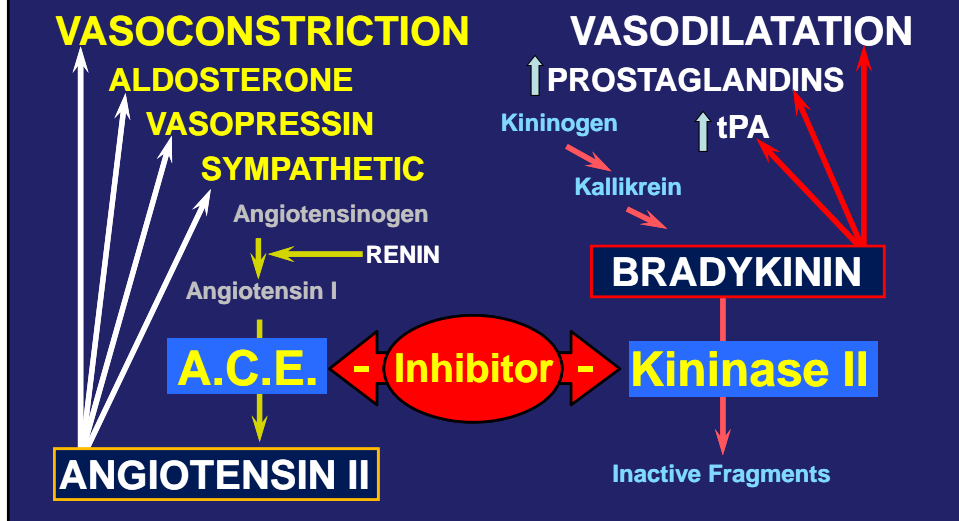
### **Spirolactone :**

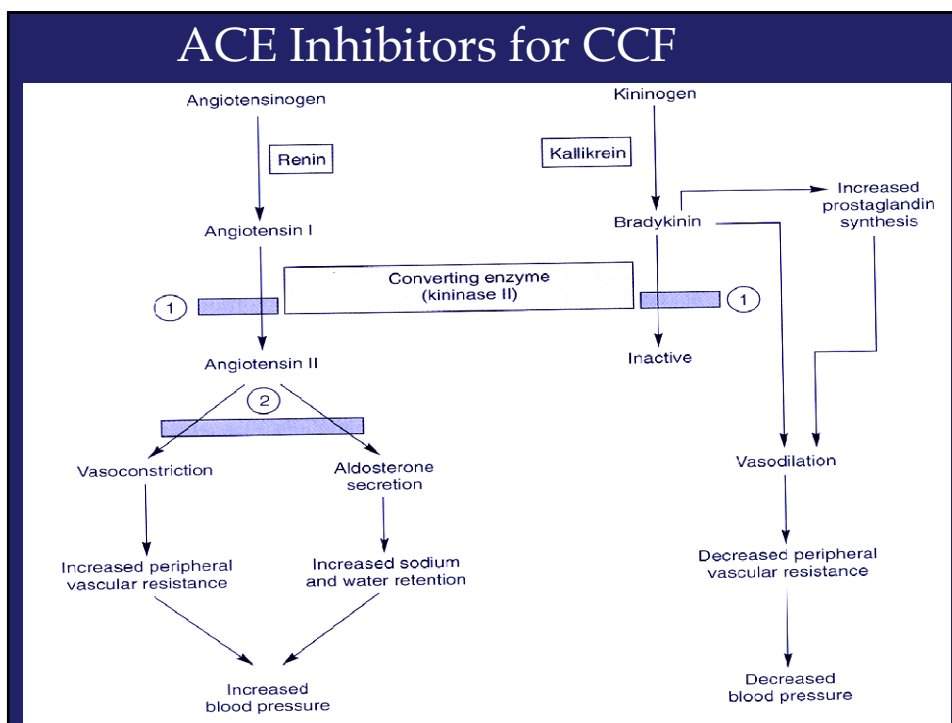
- Aldosterone inhibition
- Minimizes potassium loss,
- Prevents sodium and water retention, endothelial dysfunction and myocardial fibrosis.
- ◆ Spirolactone can be added to loop diuretics - modestly enhances diuresis,  
- Corrects hypokalemia  
Improve survival.

## ACE-I. Clinical Effects

- Improve symptoms
- Reduce remodelling / progression
- Reduce hospitalization
- Improve survival

## ACE-i. Mechanism of Action





### Angiotensin Converting Enzyme Inhibitors for CCF

ACE -I improve mortality, morbidity, exercise tolerance, left ventricular EF.

- Reduce arterial resistance (afterload)
- Reduce venous tension (preload)
- Reduce aldosterone secretion
- Inhibit cardiac and vascular remodeling  
eg Captopril, Lisinopril, Enalapril, Ramipril, .
- **Competitive Angiotensin II (AT-1) antagonists**  
Losartan, Irbesartan, Candesartan

## ACE-i. Practical Use

- Start with very low dose
- Increase dose if well tolerated
- Renal function & **serum K<sup>+</sup> after 1-2 w**
- Avoid fluid retention
- Combine with diuretic to overcome “resistance”

## ACE I

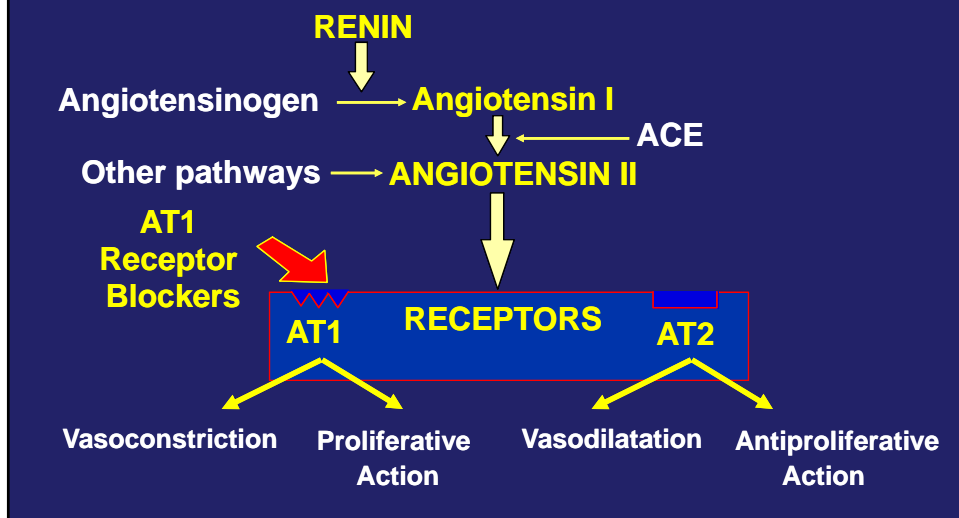
### Adverse effects

- Hypotension (1st dose effect)
- Worsening renal function
- Hyperkalemia
- Cough
- Angioedema
- Rash, neutropenia,

### Contraindications

- Intolerance (angioedema, anuria renal fail.)
- **Bilateral renal artery stenosis**
- Pregnancy
- Renal insufficiency (creatinine > 3 mg/dl)
- Hyperkalemia (> 5.5 mmol/l)
- Severe hypotension

## Angiotensin II Receptor Blockers (ARB)



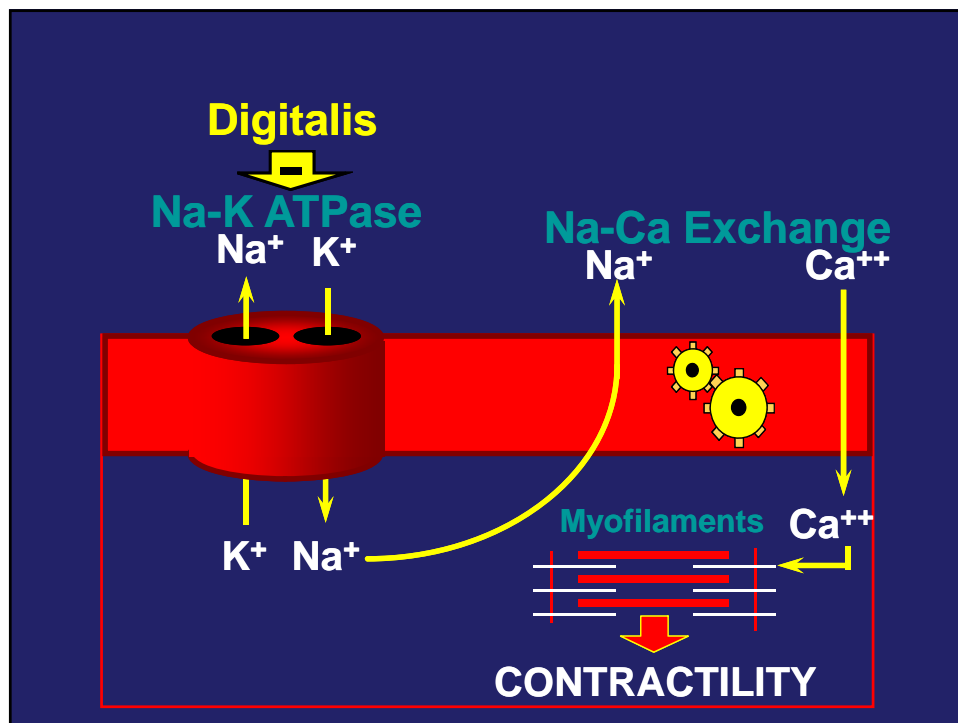
## Beta blockers for CCF

- Acts primarily by inhibiting the sympathetic nervous system.
- Increases beta receptor sensitivity (up regulation).
- Anti-arrhythmic properties.
- Anti-oxidant properties.
- Start at low dose-monitor for bradycardia
- Carvedilol, Metoprolol are most commonly used beta blockers for CCF

## Cardiac glycosides for CCF

### Digoxin :

- Inhibits Na/K ATPase pump - increase intracellular sodium concentration - and increase cytosolic calcium.
- Restores vagal tone- abolishes sympathetic over activity.
- Increases refractoriness of AV node thus decrease ventricular response to atrial rate.
- A first-line drug congestive heart failure with atrial fibrillation.



## Digitalis. Mechanism of Action

Blocks  $\text{Na}^+ / \text{K}^+ \text{ATPase} \Rightarrow \text{Ca}^{++}$

- Inotropic effect
- Natriuresis
- Neurohormonal control
  - ↓ Plasma Noradrenaline
  - ↓ Peripheral nervous system activity
  - ↓ RAAS activity
  - ↑ Vagal tone
  - Normalizes arterial baroreceptors

*NEJM 1988;318:358*

## Digoxin : Adverse effects / Precautions

- Nausea, vomiting, gynecomastia, visual disturbances and psychosis.
- Ventricular bigeminy, AV block and bradycardia.
- Amiodarone and verapamil can increase the plasma concentration of digoxin by inhibiting its excretion.
- Digoxin toxicity treatment:
- Toxicity can be treated with higher than normal doses of potassium.
- Digoxin antibody (digibind, Fab) specifically treats life-threatening digoxin overdose.

## Digitalis. Indications

- Inadequate response to ACE-i + diuretics + beta-blockers *AHA / ACC Guidelines 2001*
- If symptoms persist in combination with ACE-i + diuretics *ESC Guidelines 2001*
- Atrial Fibrillation (slows AV conduction)

## Digoxin. Contraindications

- Digoxin toxicity
- Advanced A-V block without pacemaker
- Bradycardia or sick sinus without Pacemaker
- PV beats and VT
- Marked hypokalemia
- W-P-W with atrial fibrillation

## $\beta$ -Adrenergic Blockers Mechanism of action

- $\uparrow$  Density of  $\beta_1$  receptors
- Inhibits cardiotoxicity of catecholamines
- $\downarrow$  Neurohormonal activation
- $\downarrow$  HR, remodelling & myocardial  $O_2$  consumption.
- Anti-ischemic
- Antihypertensive
- Antiarrhythmic
- ‘Antioxidant, Antiproliferative’

Decrease frequency of ischemic events / potential for lethal arrhythmias,

$\beta$ -Blockers may resensitize down-regulated receptor, improve myocardial contractility.

Contraindication – Unstable cardiac status



## **β-Adrenergic Blockers Clinical Effects**

- Improve symptoms (only long term)
- Reduce remodelling / progression
- Reduce hospitalization
- Reduce sudden death
- Improve survival

### **After AMI**

Beta-blockers (bisoprolol, carvedilol, sustained metoprolol) and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF.

## **β-Adrenergic Blockers Adverse Effects/ Contraindications**

- Hypotension
- Fluid retention / worsening heart failure
- Fatigue
- Bradycardia / heart block
- Review treatment (+/- diuretics, other drugs)
- Reduce dose
- Consider cardiac pacing
- Discontinue beta blocker in severe cases

Asthma (reactive airway disease)

AV block (unless pacemaker)

Symptomatic hypotension / Bradycardia

Diabetes is NOT a contraindication

## Labetalol versus Carvedilol

- Labetalol and carvedilol both block  $\alpha_1$  receptors and thus have vasodilating properties.
- However, long-term treatment with labetalol may result in the loss of blockade of  $\alpha_1$ -receptors, leaving blockade of  $\beta$ -receptors as the major action. This effect does not occur with carvedilol.
- Labetalol has been associated with excessive vasodilation in patients with heart failure.
- **Carvedilol produces a less potent vasodilator response than does labetalol because of its modest  $\alpha_1$ adrenergic blocking ability.**
- Additionally, unlike carvedilol, the effects of labetalol on long-term morbidity and mortality are unknown

## Aldosterone Inhibitors

### Spironolactone

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

### ALDOSTERONE

- Retention  $\text{Na}^+$  → **Edema**
- Retention  $\text{H}_2\text{O}$
- Excretion  $\text{K}^+$  → **Arrhythmias**
- Excretion  $\text{Mg}^{2+}$

- Collagen deposition → **Fibrosis**
  - myocardium
  - vessels

### **Spironolactone. Indications**

- Recent or current symptoms despite ACE-i, diuretics, dig. and  $\beta$ -blockers

*AHA / ACC HF guidelines 2001*

- Recommended in advanced heart failure (III-IV), in addition to ACE-i and diuretics

- Hypokalemia

*ESC HF guidelines 2001*

### **Spironolactone. Practical use**

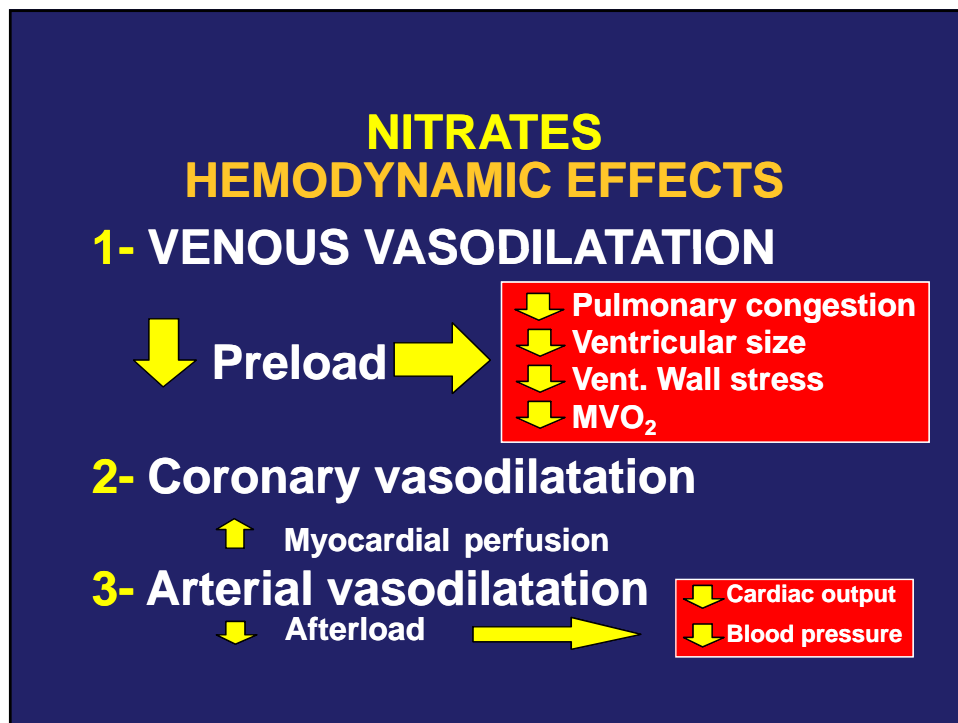
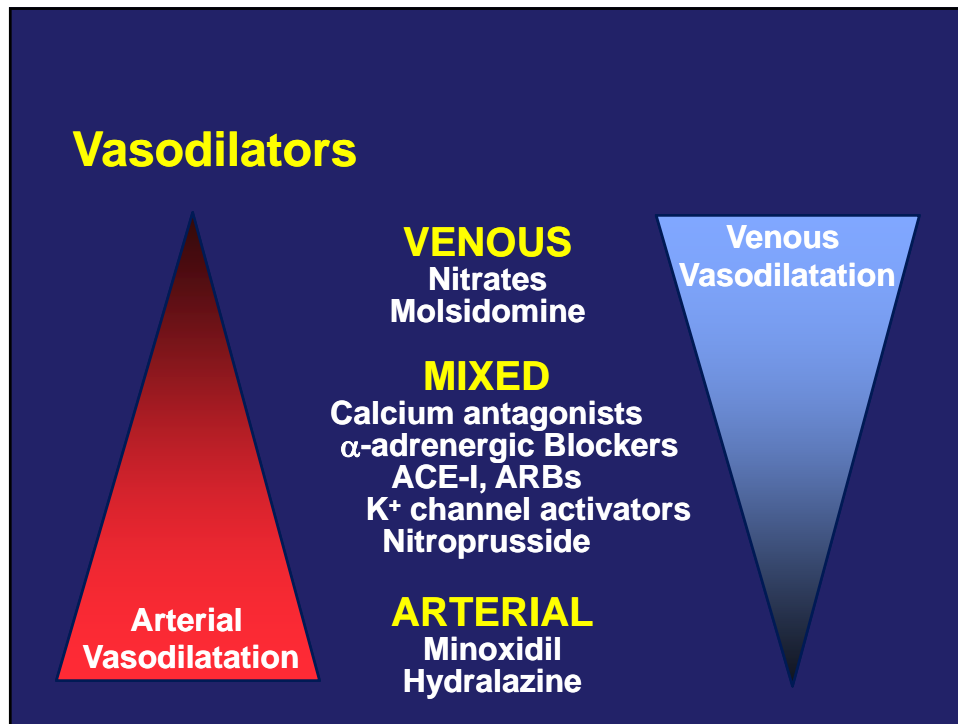
- Do not use if hyperkalemia, renal insuf.
- Monitor serum  $K^+$  at “frequent intervals”
- Start ACE-i first
- Start with 25 mg / 24h
- If  $K^+ >5.5$  mmol/L, reduce to 25 mg / 48h
- If  $K^+$  is low or stable consider 50 mg / day

## Other Drugs - in selected patients

- Inotropes: refractory HF
- Nitrates: ischemia, angina, pulmonary congestion
- ARB: Contraindications to ACE-i
- Antiarrhythmics: (only amiodarone) H risk arrhyth.
- Anticoagulants: High risk of embolism
- Statins : modulators of arterial resistance

## Vasodilators for CCF

- Isosorbide dinitrate and hydralazine also used specially in patients who cannot tolerate ACE inhibitors.
- **Amlodipine** (Caution) and prazosin are other vasodilators used in CCF.



## Nitrates. Clinical Use

- CHF with myocardial ischemia
- Orthopnea and paroxysmal nocturnal dyspnea
- In acute CHF and pulmonary edema: NTG sl / iv
- Nitrates + Hydralazine **in intolerance to ACE-I (hypotension, renal insufficiency)**

A combination of hydralazine and a 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.

## Positive Inotropic Therapy

- **Phosphodiesterase III Inhibitors**  
Positive inotropic & vasodilator – INO-DILATOR  
Eg., Milrinone
- **Dobutamine** selective  $\beta_1$  agonist- +ve inotropic/CO
- **Dopamine** Non-selective  $\beta_1$  agonist – preserves RBF
- **May increase mortality**  
Exception: Digoxin, Levosimendan
- **Use only in refractory CHF**
- **NOT for use as chronic therapy**

**Drugs to Avoid** (may increase symptoms, mortality)

- Inotropes, long term / intermittent
- Antiarrhythmics (except amiodarone)
- Calcium antagonists (except amlodipine)
- Non-steroidal antiinflammatory drugs (NSAIDS)
- Tricyclic antidepressants
- Corticosteroids
- Lithium

*ESC HF guidelines 2001*

## Drugs for CCF

### Conclusion :

- ACE inhibitors are cornerstone in the treatment of CCF.
- Beta blockers are used in selected patients (mild/moderate failure, low dose)
- Diuretics and digoxin are other drugs useful in CCF in select patients.