



Pathophysiology and Treatment of Heart Failure



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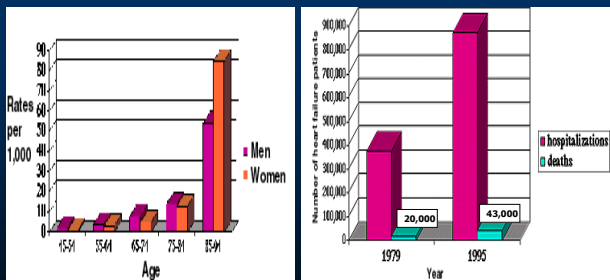
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The Issues to Discuss

- ◆ Incidence of HF
- ◆ Pathophysiology of HF
- ◆ Treatment of HF
 - evidence-based medicine and results of clinical trials

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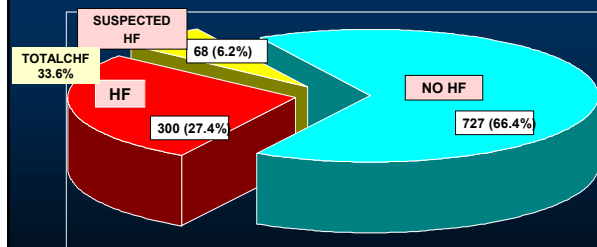
Epidemiology of Heart Failure



500,000 new cases of HF per year in USA

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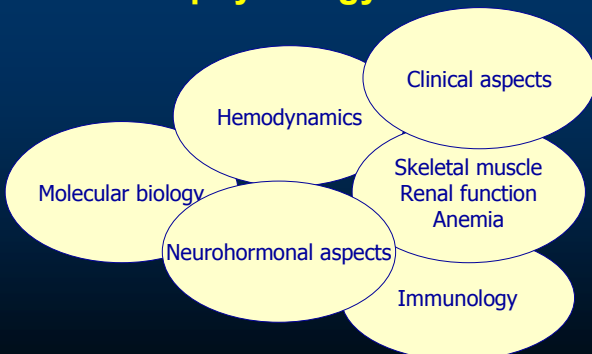
Prevalence of HF in Pts Hospitalized in Internal Med and Cardiology Depts in Haifa



Data from LDCMC registry and Euro Heart Survey (Lewis et al, J Isr Heart Soc 2003;13:40)

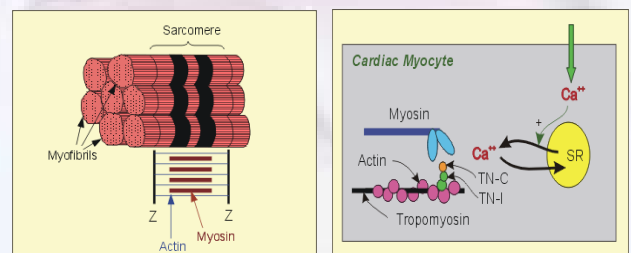
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Pathophysiology of HF



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Myocardial Function: Molecular Biology



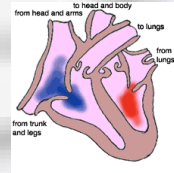
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Hemodynamics: Ventricular function

Abnormalities of ventricular function:

Systolic function

Diastolic function

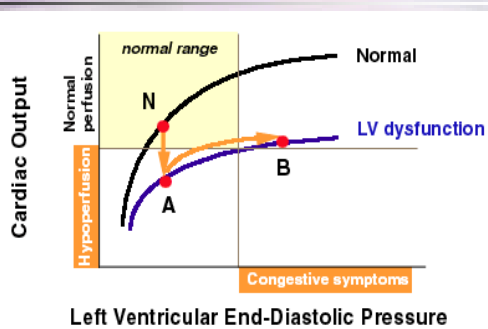


Assessment of LV Contractility

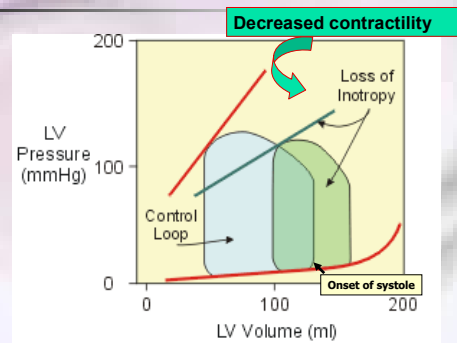
Assessment of myocardial contractility is based on relations between

- Force
- Velocity
- Fiber length

Systolic Function: Starling Curves



The Pressure-Volume Loop



LV Wall Stress and LV Hypertrophy

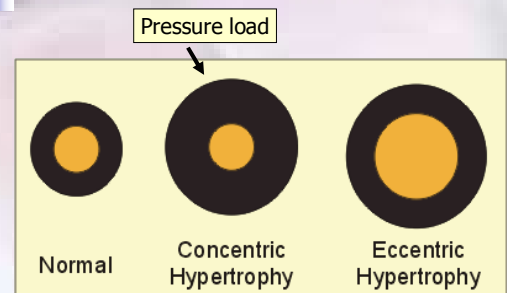


$$\text{Stress} = \frac{P \times R}{2W}$$

- Wall stress:
- circumferential
 - meridional
 - radial
- tends to remain=k

FIGURE 15-8. Circumferential (σ_c), meridional (σ_m), and radial (σ_r) components of left ventricular wall stress from an elliptical model.

Wall Stress and LVH



LV Wall Stress and LV Hypertrophy

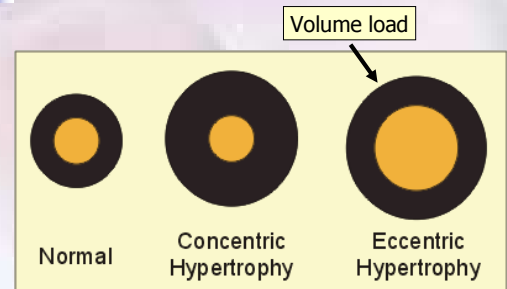


$$\text{Stress} = \frac{P \times R}{2W}$$

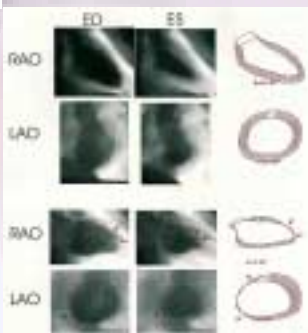
- Wall stress:
- circumferential
 - meridional
 - radial
- tends to remain=k

FIGURE 15-8 Circumferential (σ_c), meridional (σ_m), and radial (σ_r) components of left ventricular wall stress from an elliptical model.

Wall Stress and LVH



Regional Wall Motion



Global LV function and dysfunction

- Regional LV dysfunction
- hypokinesis
 - akinesis
 - dyskinesis
- regional asynchrony

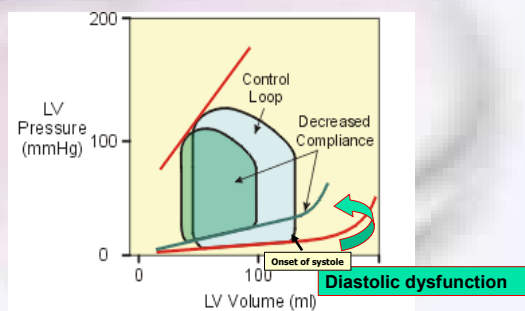
Diastolic Dysfunction

- Decreased ventricular compliance
- Increased LV end-diastolic pressure
- Increased LA pressure and pulmonary venous pressure
- Interstitial edema, intra-alveolar edema
- Shortness of breath, pulmonary edema

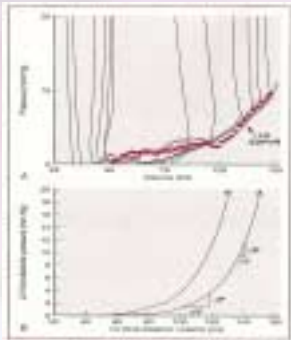
Diastolic Dysfunction: Etiology

- LV hypertrophy
 - Hypertension
 - Aortic valve disease
 - Hypertrophic heart disease
- Fibrosis
 - Post-myocardial infarction, other
- Ischemia
 - Coronary artery disease

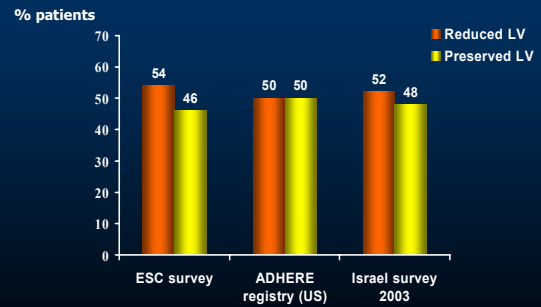
The Pressure-Volume Loop



Diastolic function: The P-V relation

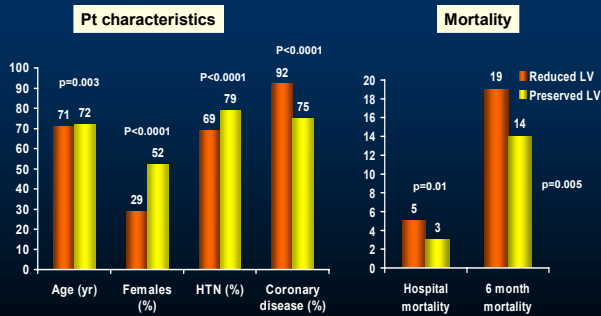


Preserved LV Function in HF Patients (Diastolic dysfunction)



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HF with Preserved LV Function: The Israel National HF Survey 2003



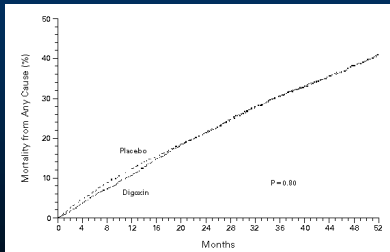
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Clinical Trials for HF: Where Do We Stand?

- ◆ Digoxin
- ◆ ACE inhibitors
- ◆ Angiotensin II receptor antagonists
- ◆ Beta blockers
- ◆ Aldosterone antagonists
- ◆ New drugs - Endothelin antagonists, other
- ◆ Non-pharmacologic therapies

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Effect of Digoxin on All-cause Mortality

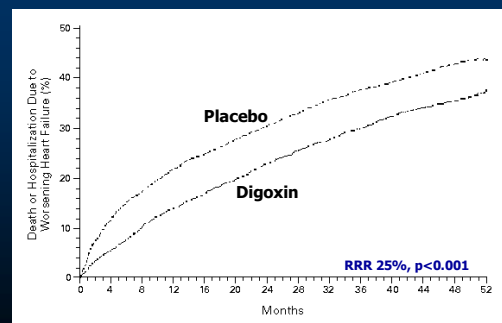


No. of Patients at Risk:
 Placebo 3468 3239 3105 2976 2840 2709 2652 2551 2305 1891 1506 1160 734 389
 Digoxin 3397 3269 3144 3019 2892 2759 2644 2531 2384 1840 1475 1156 737 335

DIG investigators, NEJM 1997; 336:525-33

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Effect of Digoxin on Death/Hospitalization for Worsening Heart Failure



DIG investigators, NEJM 1997; 336:525-33

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Adjusted Outcomes (Hazard Ratios) by Serum Digoxin Levels

Adjusted outcomes*	Placebo	HR (0.5-0.8 ng/mL)	HR (0.9-1.1 g/mL)	HR (≥1.2 ng/mL)
All-cause mortality	Referent	0.80	0.89	1.16
Cardiovascular mortality	Referent	0.86	0.93	1.21
Worsening heart failure	Referent	0.66	0.86	0.95
All-cause hospitalization	Referent	0.83	1.02	0.90
Hospitalization for worsening heart failure	Referent	0.56	0.74	0.65

Rathore SS et al. JAMA 2003;289:871-878



Digoxin: What Have We Learnt?

- Digoxin improves symptoms and decreases hospitalizations
- Dig withdrawal may cause worsening of symptoms
- No survival benefit in the DIG trial, but this may have been due to pro-arrhythmia in pts with high serum dig levels

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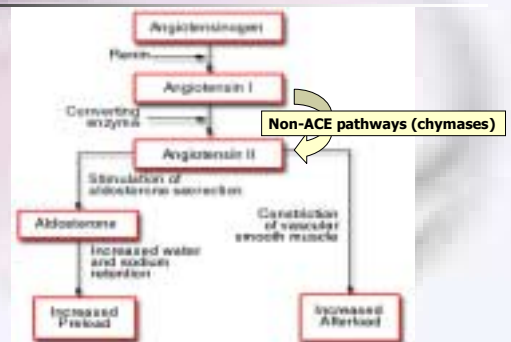


Neurohormonal Effects in HF

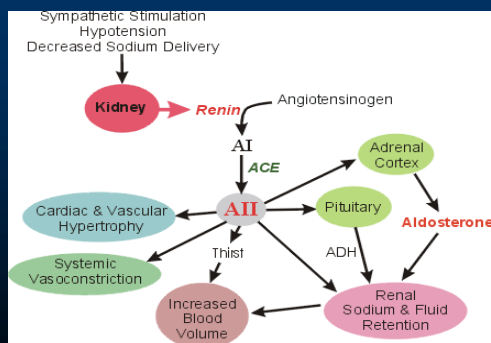
Angiotensin II Norepinephrine

- Hypertrophy, apoptosis, ischemia, arrhythmia, remodelling, fibrosis
- Vasoconstriction, afterload

Renin – Angiotensin – Aldosterone System (RAAS)



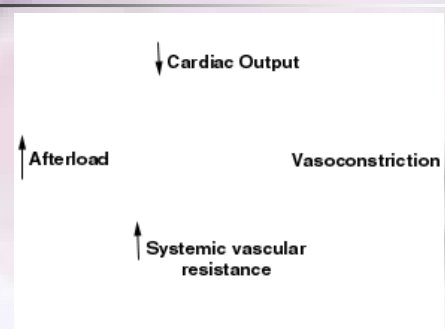
Effects of Angiotensin II – The Bad Guy



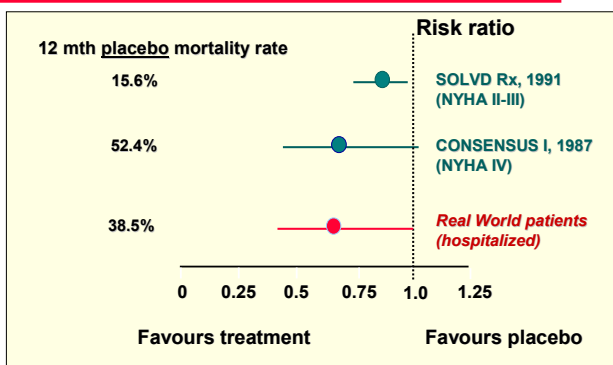
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The Neurohormonal Response



Effect of ACE-Inhibitor on Mortality



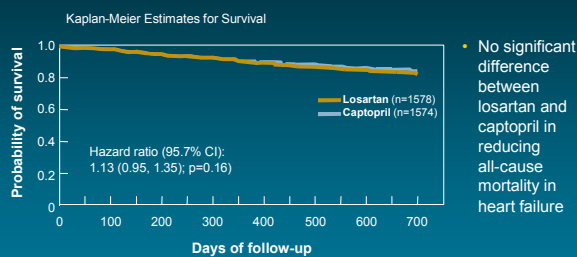
ACE-inhibitors: What Have We Learnt?

- ACE-inhibitors carry survival benefit
 - with *reduced LV* function
 - post-MI (SAVE, others)
 - high risk pts, even *without CHF or reduced LVEF* (HOPE study)
- Mechanisms
 - *Hemodynamic* effect
 - *Myocardial* effect (anti-proliferative, anti-fibrosis, anti-apoptosis)
 - *Vascular* effect (anti-atherosclerosis)
 - *Renal* protection

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The Losartan Heart Failure Survival Study–ELITE II

Primary Endpoint: All-Cause Mortality

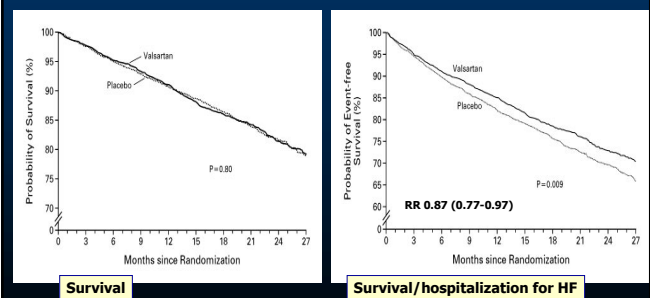


CI = confidence interval
Adapted from Pitt B et al *Lancet* 2000;355:1582-1587.



VAL-HeFT Trial: Benefit of Valsartan Added to HF Treatment

5010 pts with HF (NYHA II-IV)



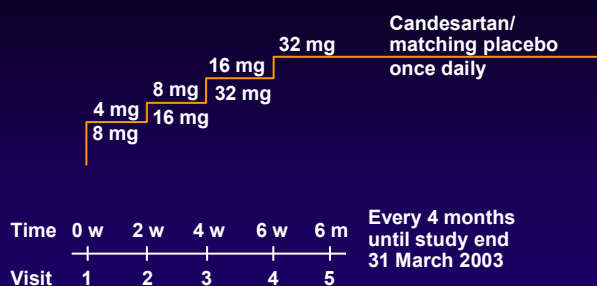
Cohn et al, *NEJM* 2001;345:1667-75

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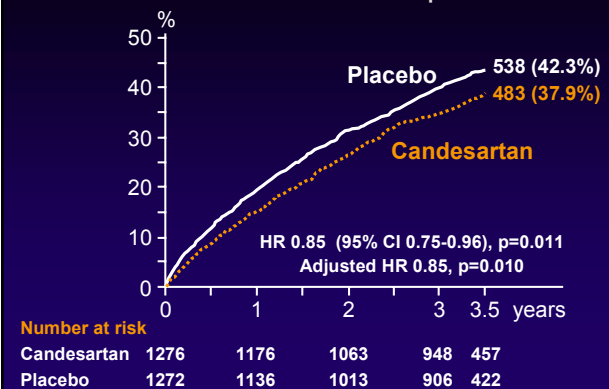
Study design

Dose-titration and visit schedule



CHARM-Added: Primary outcome

CV death or CHF hospitalisation

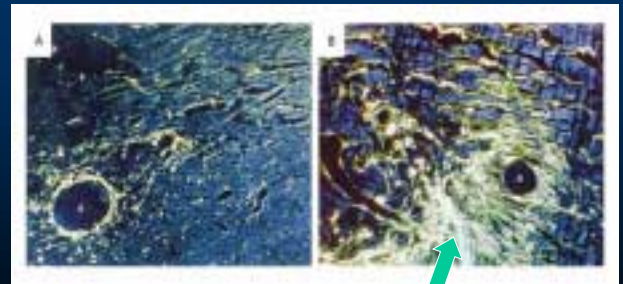


ARB's: What Have We Learnt?

- ARB's carry survival benefit
 - In pts who do not tolerate ACE-inhibitors
 - May improve morbidity in those already receiving ACE-inhibitors
 - Should be used instead of ACE-inhibitors in pts post-MI or HF where necessary
- In hypertension
 - Are superior to beta-blocker based Rx with regard to CNS effect
 - Decreased stroke, mental deterioration (LIFE, SCOPE)

EFFECT OF ALDOSTERONE

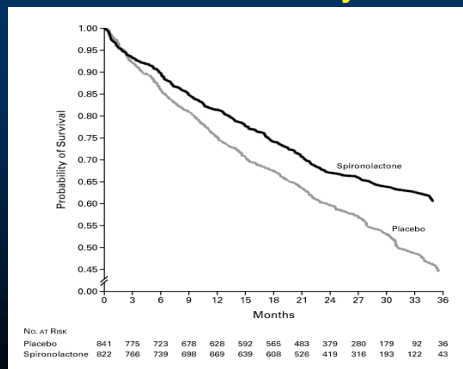
Normal heart Aldosterone (plus salt)



Weber, NEJM 2001;345:1689-1697

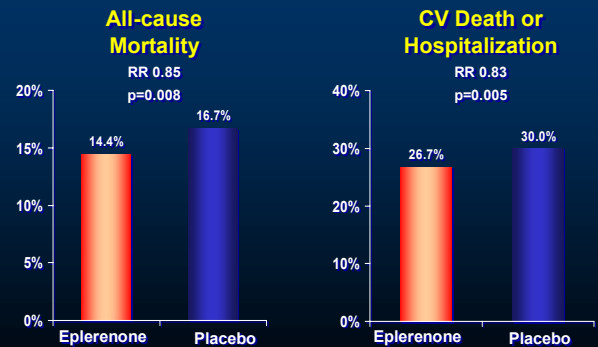
Perivascular fibrosis

Effect of Spironolactone in CHF: The RALES Study

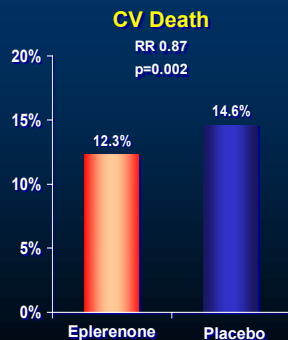


EPHESUS Trial: Primary Endpoints

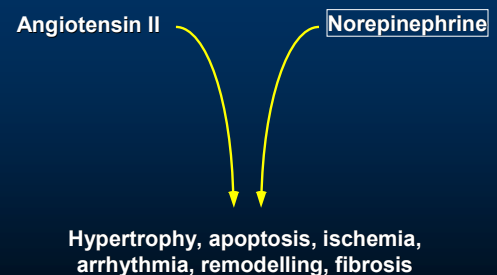
6632 pts post-AMI, with LV dysfunction and HF

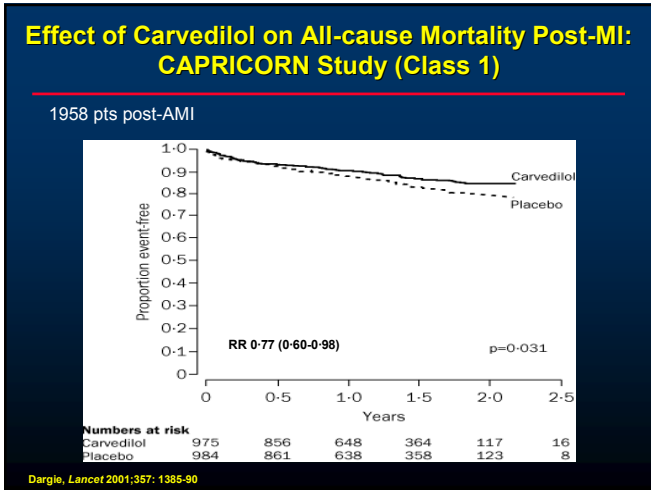
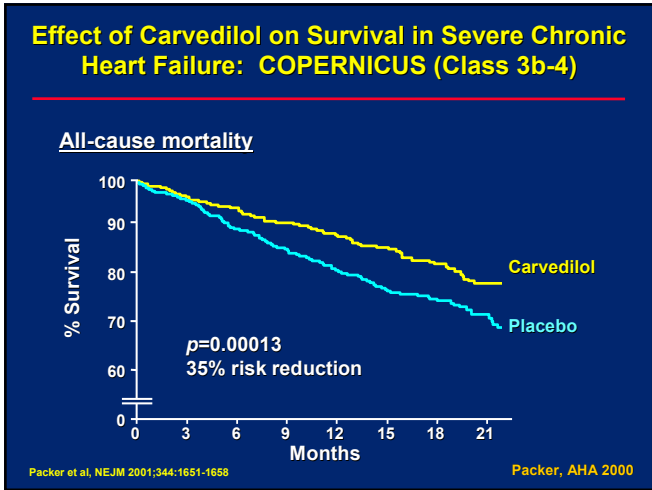
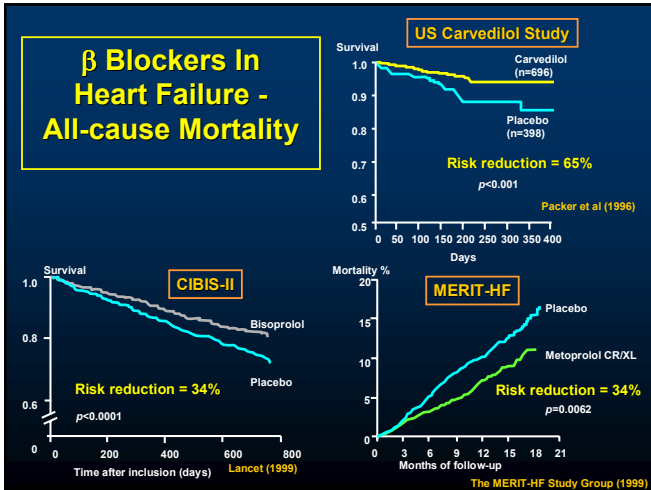


EPHESUS Trial: Secondary Endpoint



NEUROHORMONAL EFFECTS IN HF



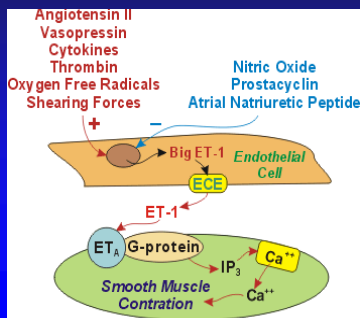


- ### Beta Blockers for HF and LV Dysfunction: What Have we Learnt?
- Beta blockers indicated for pts with class 2-3 HF (US and NZ carvedilol; CIBIS; MERIT)
 - Carvedilol indicated in pts with Class 3-4 HF (Copernicus)
 - Carvedilol indicated for post AMI pts with LVEF < 40% (Capricorn)
 - Pts should be stable, no fluid overload, dose increased gradually

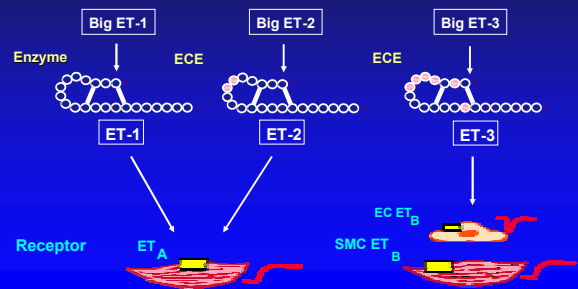
- ### Established Pharmacotherapy For Heart Failure: Summary
- ♦ Digoxin
 - ♦ Diuretics
 - ♦ ACE inhibitors
 - ♦ Angiotensin II receptor antagonists
 - ♦ Beta blockers
 - ♦ Aldosterone antagonists
 - ♦ Other Rx – Drugs, Devices, Surgical
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- ### Other Approaches and Studies
- ♦ **Endothelin antagonists**
 - Bosentan, tezosentan
 - ♦ **ANP system**
 - Nesiritide (BNP type substance)
 - ♦ **Immune system**
 - antagonize TNF-α (Enbrel), modulate immune response
 - RESTORE study, VASOGEN-ACCLAIM study
 - ♦ **Treat anemia**
 - Erythropoietin, Fe
 - ♦ **Mechanical devices, surgical approaches**
 - Pacing and synchronous (biventricular) pacing
 - LVAD's, newer surgical approaches
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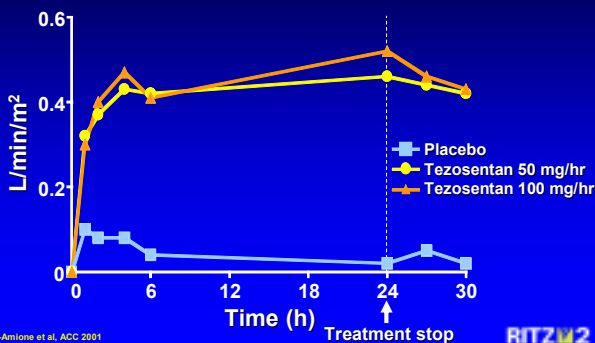
The Endothelin System



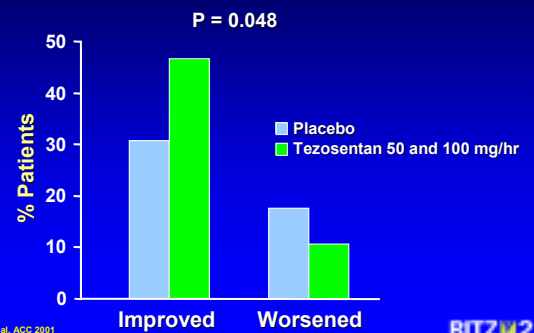
The Endothelin System



RITZ-2: Cardiac Index Change From Baseline Over Time



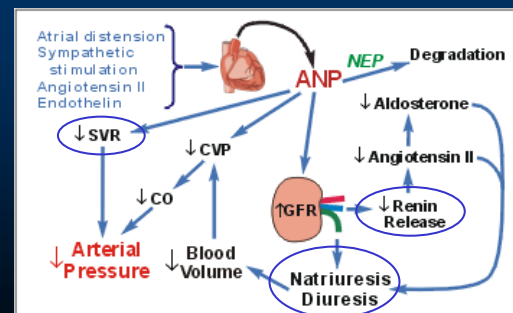
RITZ-2: Dyspnea Score at 24 Hours (Seven-point Scale)



Endothelin Antagonists in HF: The ENABLE Study

- 1400 pts with Class 3-4 CHF
- Bosentan (62.5-125mg b.i.d.) for >18 mths
- Primary end-point: all-cause mortality or hospitalization for CHF
- Secondary: clinical status at 9 mths
- **No additional benefit**

ANP System: Nesiritide (Noratak)



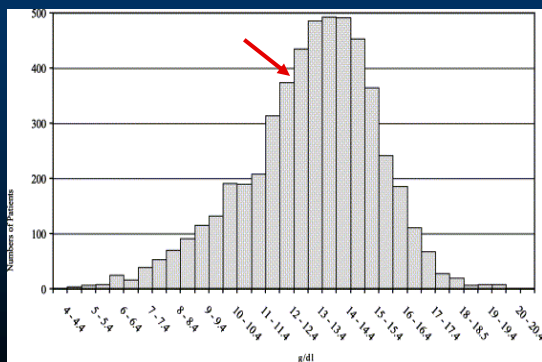
Immune Modulation in HF

- TNF- α is upregulated in myocardium of pts with HF
- Circulating TNF- α levels are elevated in HF
- TNF- α is associated with depressed myocardial function, cachexia
- TNF- α antagonists (enbrel, etanercept) so far have failed (RESTORE study)
- ACCLAIM study of immunomodulation currently in progress

Anemia in Heart Failure: Etiology

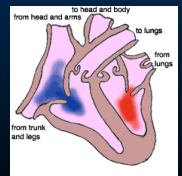
- Blood loss
- Dietary, lack of absorption
- Renal failure
 - common disease process (atheroma, HTN, DM)
 - pre-renal
- Resistance to erythropoietin (TNF- α)
- Unrelated causes

Hemoglobin values recorded in 5249 (92% of total enrolled) men in EuroHeart Failure survey

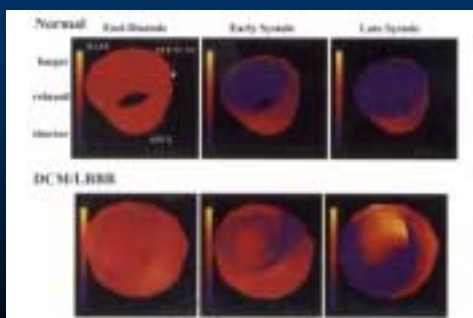


Anemia: Hemodynamics

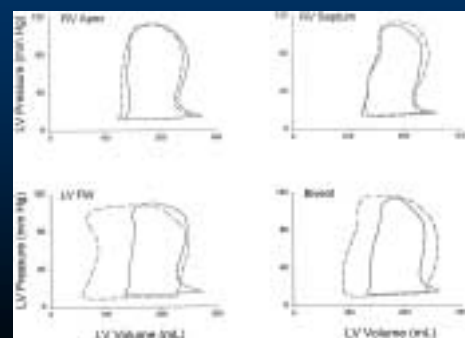
- Decreased O₂ transport capacity
- Vasodilatation, increased cardiac output
- Volume overload
- Implications for LV function
 - Systolic function
 - Diastolic function



Device Therapy for HF: Cardiac Resynchronization (CRT) for Pts with LBBB



Effect of Pacing Site on LV Function: Pressure-Volume Loops



Surgical treatments for CHF

- Revascularization for ischemic/hibernating myocardium
- LV aneurysmectomy/remodeling (Dor)
- LV resection (Batista procedure)
- Cardiomyoplasty
- LV assist devices
- Transplantation



Improved Clinical Outcome in HF

- 1 year mortality (Class 4 pts)
 - 1987 (CONSENSUS 1)
 - **52%** (placebo arm)
 - 2000 (MERIT-HF)
 - **17%** (treatment arm)



Drug Treatment of Heart Failure 1974-2004

Old treatment (1974)	New treatment (2004)	Failed treatments
Digoxin	Digoxin	Milrinone
Diuretic	Diuretic	Xamoterol
	ACE inhibitor/ARB	Flosequinan
	Beta blocker	Vesnarinone
	Aldosterone antagonist	Pimobendan
		Flolan
		Sotalol
		Bosentan
		Omapatrilat
		Enbrel (anti TNF)



Thank you



- Pfizer Israel - for their never-ending support
- All of you for listening

Fall 2004

