심부전의 병태 생리 및 만성 심부전의 약물치료

강 석 민

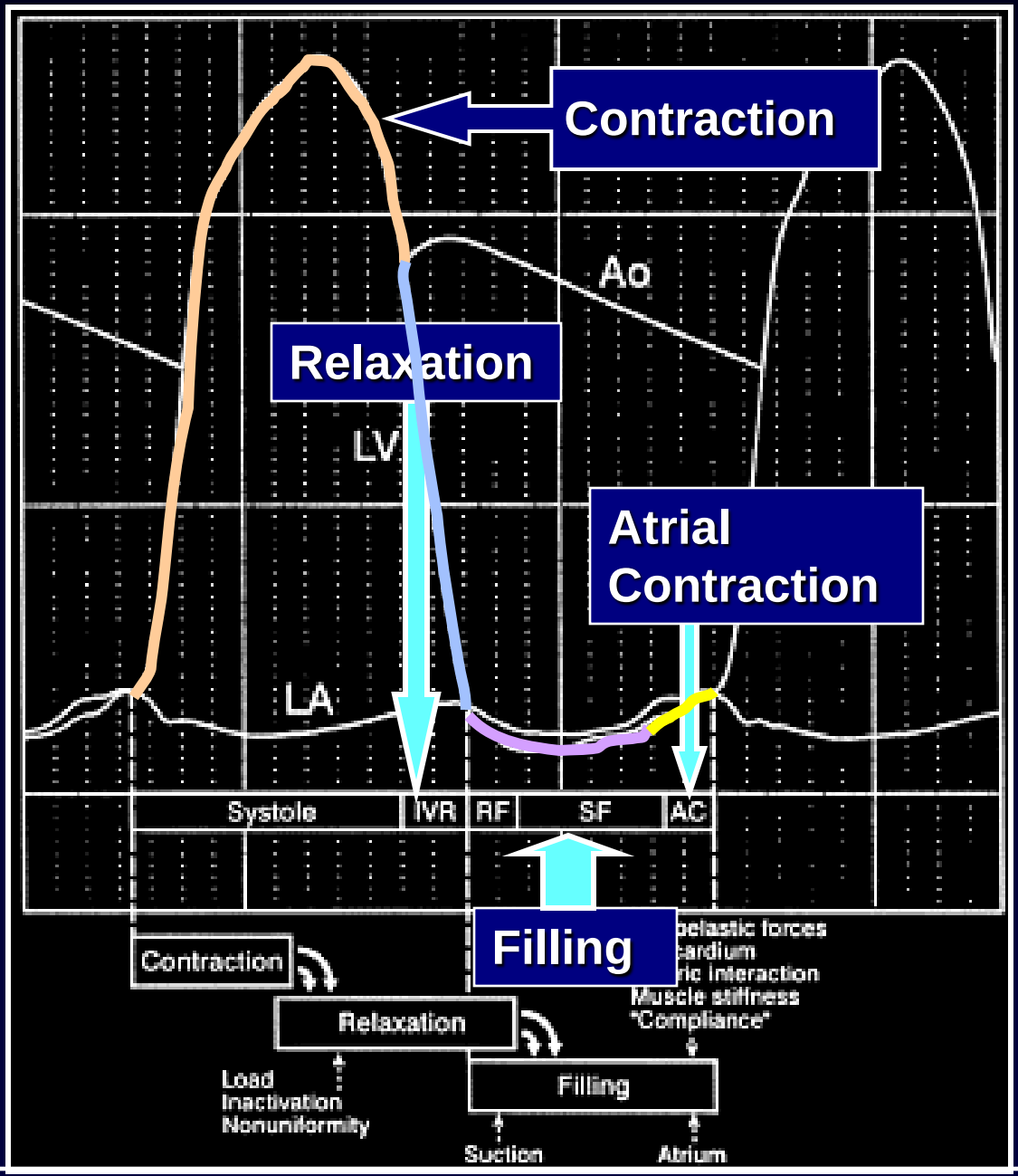
연세의대 심장내과

Contents

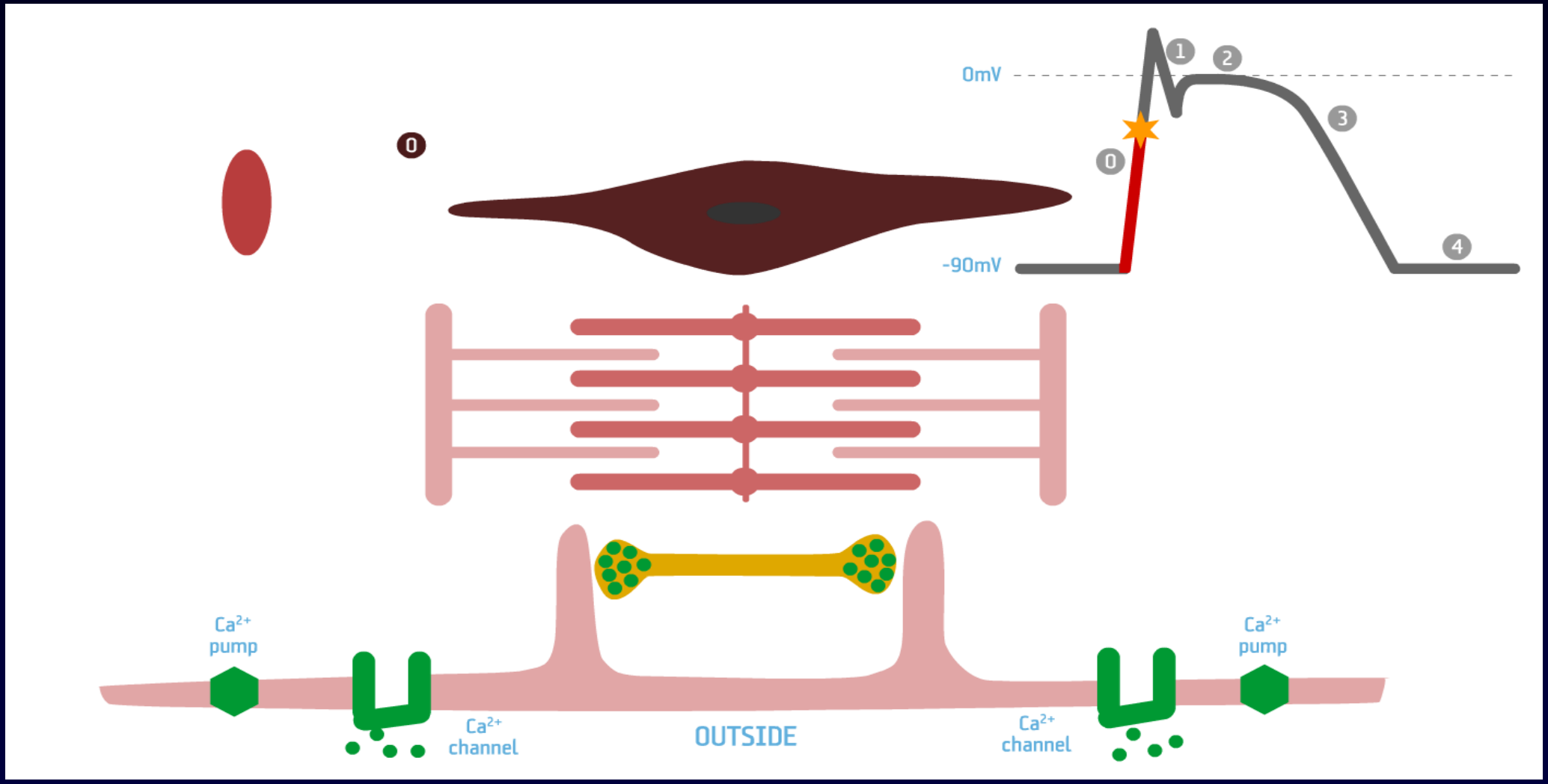
- Review cardiac physiology and pathophysiology of CHF
- Current guideline for medical Tx. of CHF

Cardiac cycle:

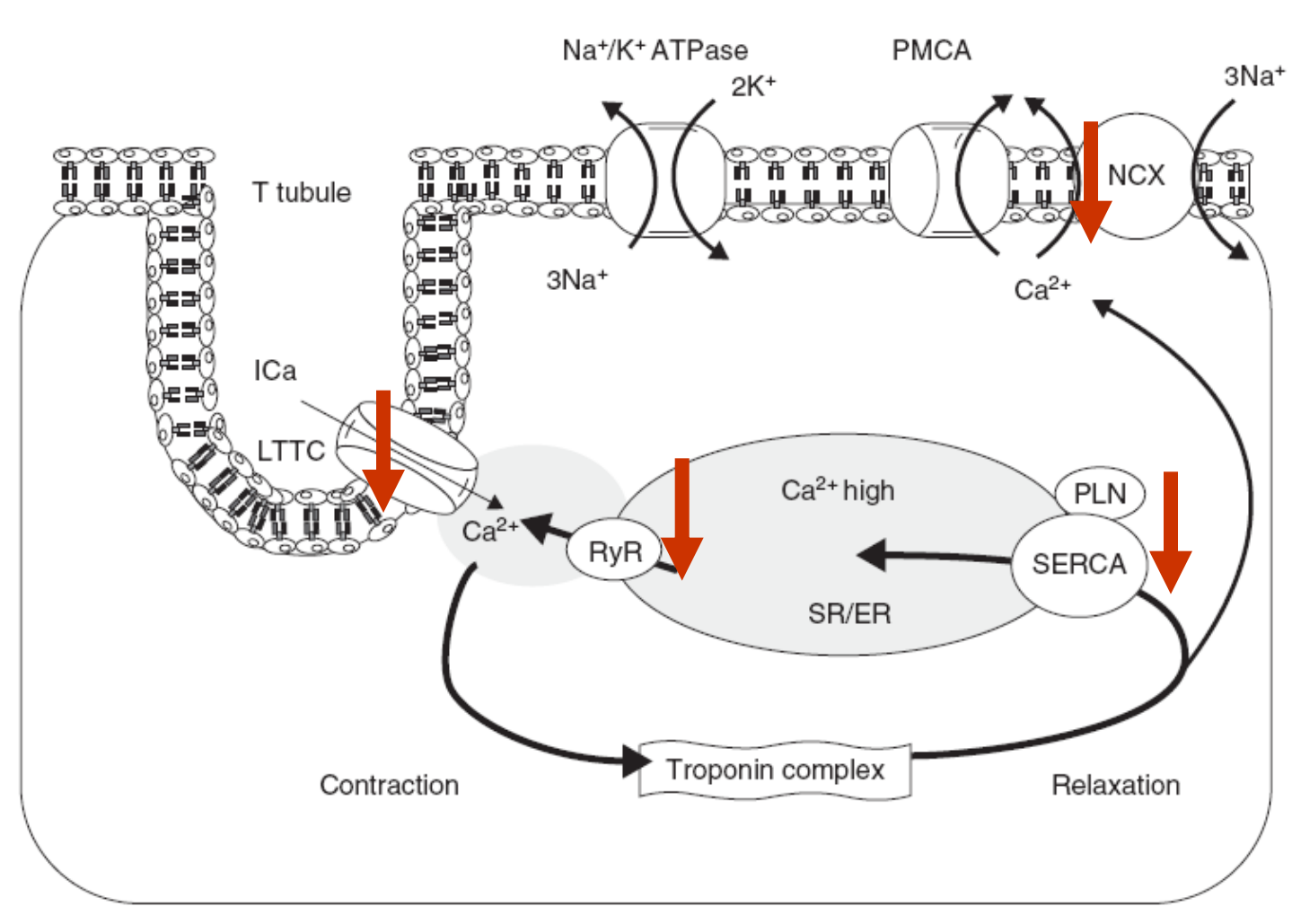
- Contraction
- Relaxation
- LV Filling
- Atrial Contraction



Excitation-Contraction coupling



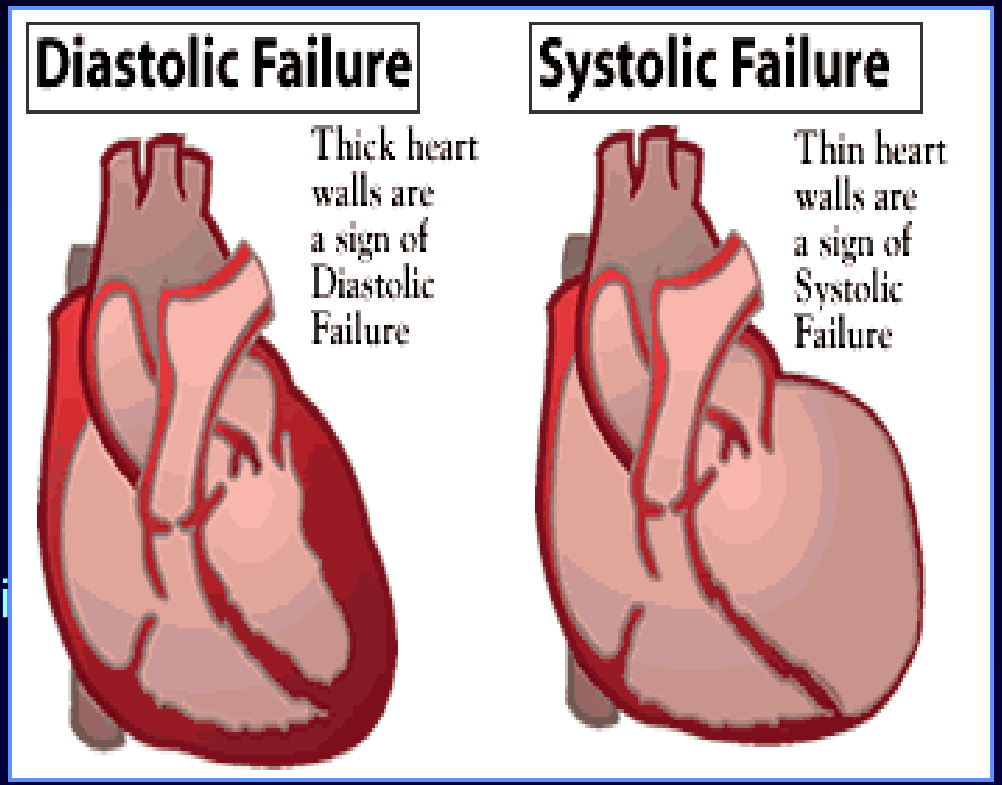
Alterations in Excitation-Contraction coupling



Expert Opin. Biol. Ther. 2010;10:29-41

Systolic vs. Diastolic

- **Diastolic dysfunction**
  - EF normal or increased
  - Hypertension
  - Due to chronic replacement fibrosis ischemia-induced decrease in distensibility
- **Systolic dysfunction**
  - EF < 40%
  - Usually from coronary disease
  - Due to ischemia-induced decrease i contractility
- Most common is a combination of both



Three Pathophysiological Causes of Heart Failure

- Increased work load (pre & afterload)

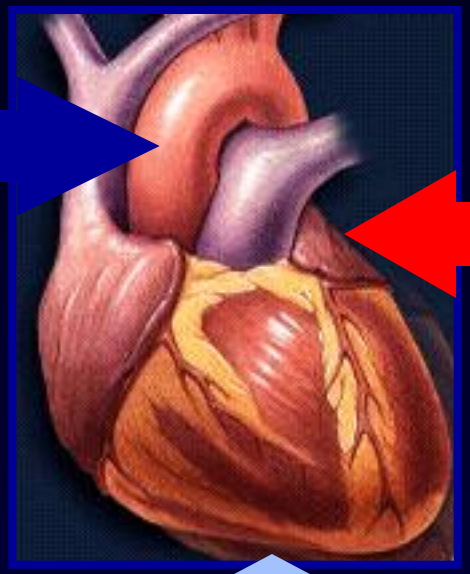
- Myocardial Dysfunction (systolic and/or diastolic)

- Decreased Ventricular Filling

Determinants of Stroke Volume

Afterload (arterial pr.)

- Vasodilators
- ACE inhibitors
- ARBs



Preload (venous pr.)

- Diuretics
- Nitrates

Contractility

- Inotropics

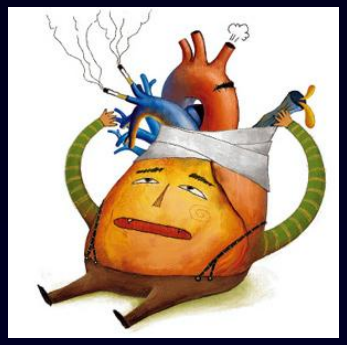
Cardiac Output = Stroke Volume

X

Heart Rate

Compensatory Mechanisms

- ***Increased Heart Rate***
  - Sympathetic = Norepinephrine
- ***Dilation***
  - Frank Starling = Contractility
- ***Neurohormonal Activation***
  - Redistribution of Blood to the Brain



Decompensation

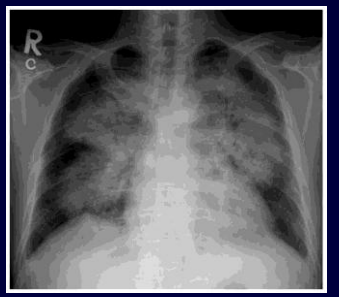
Increased Pulmonary Venous Pressure (PAWP)

↓

Interstitial Edema

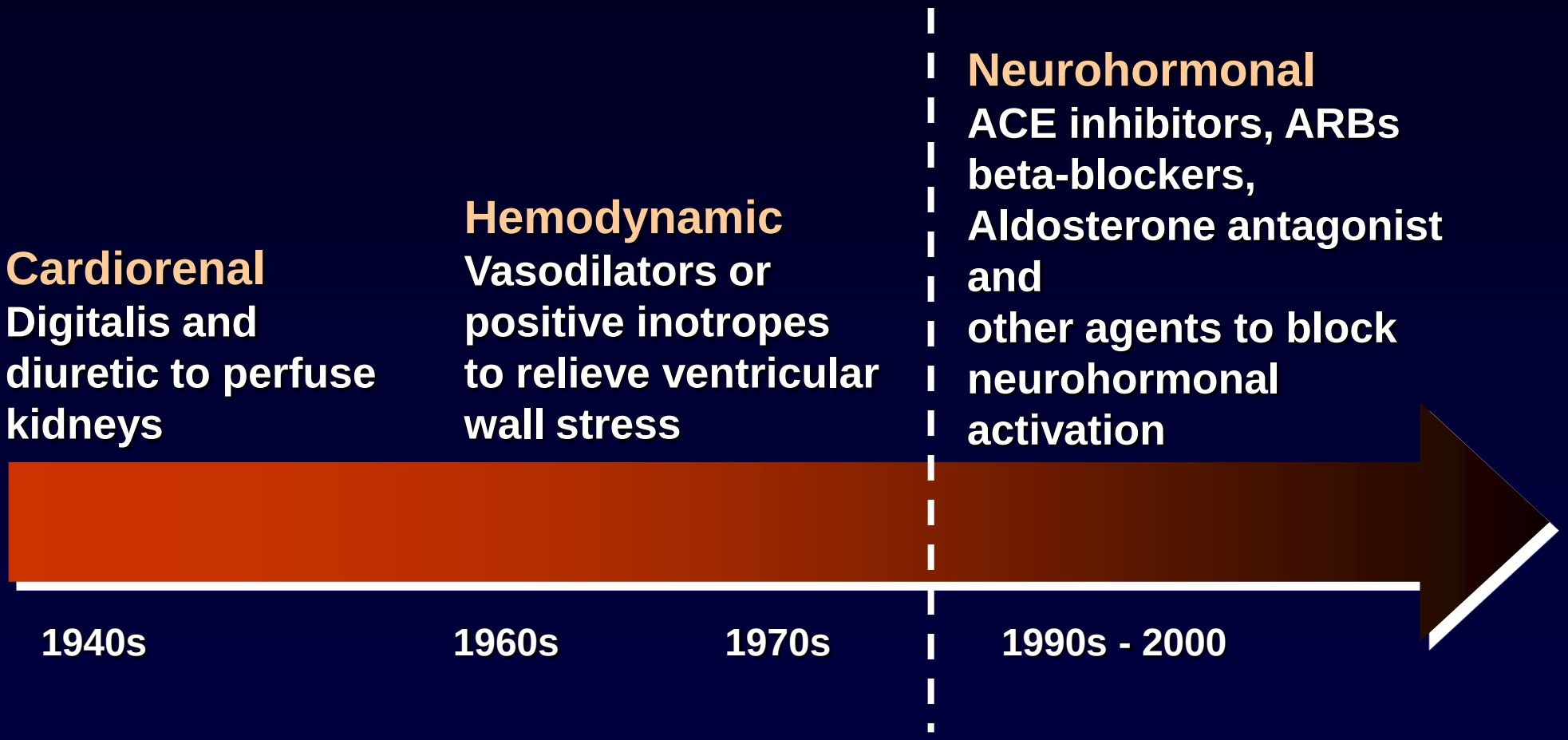
↓

Alveolar Edema



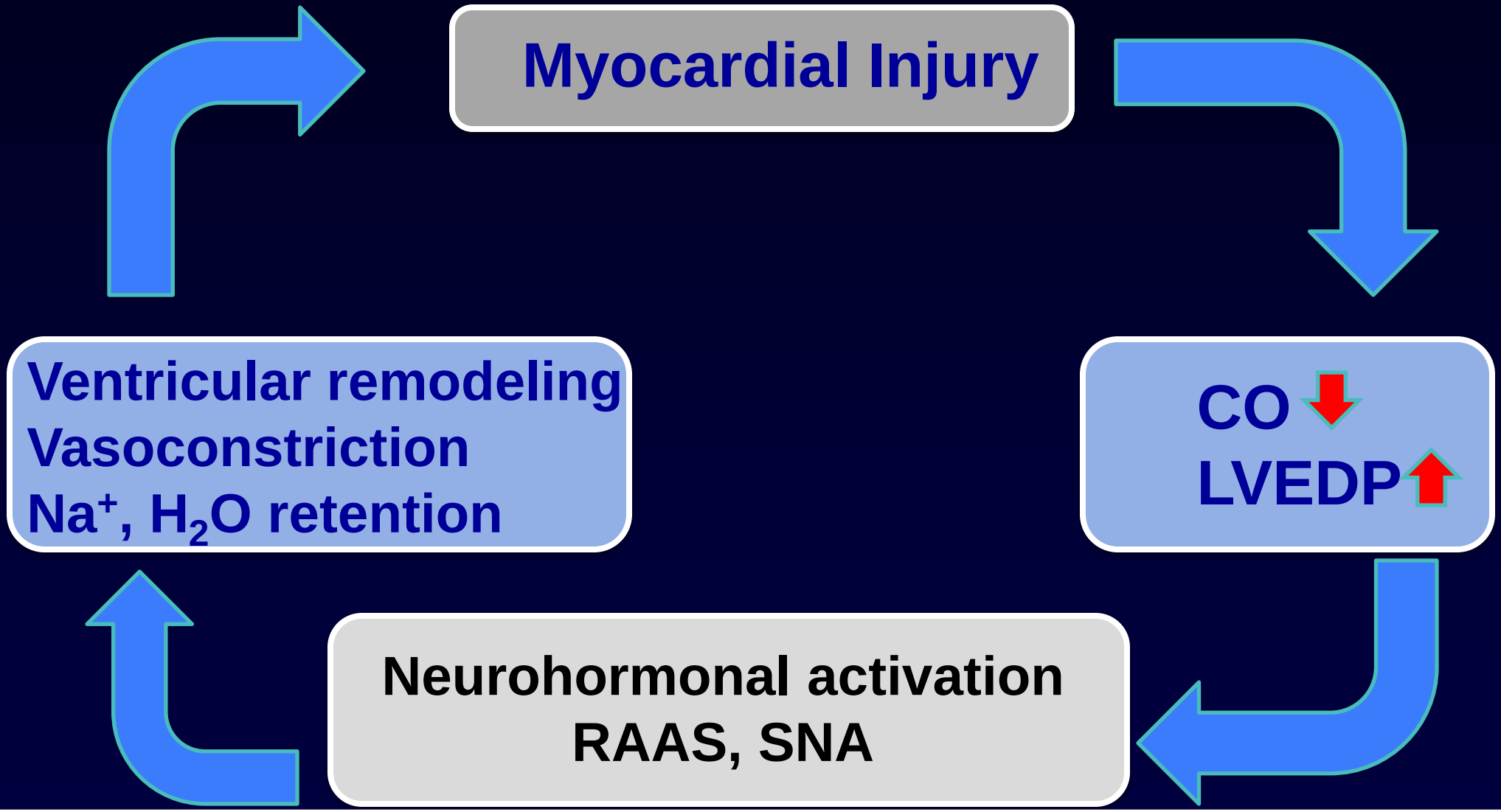

Symptoms are Just the Tip of the Iceberg
Orthopnea
Fatigue
Dyspnea
Edema
Events
Symptoms
Systemic congestion
(JVD, edema)
Increased RV and RA pressure
Increased PA pressure
Increased PCWP (congestion)
Increased LA and LVEDP
↑ LVEDP + impaired volume regulation
Abnormal LV function (systolic and/or diastolic)
Alaska, 2006

심부전 개념의 변화

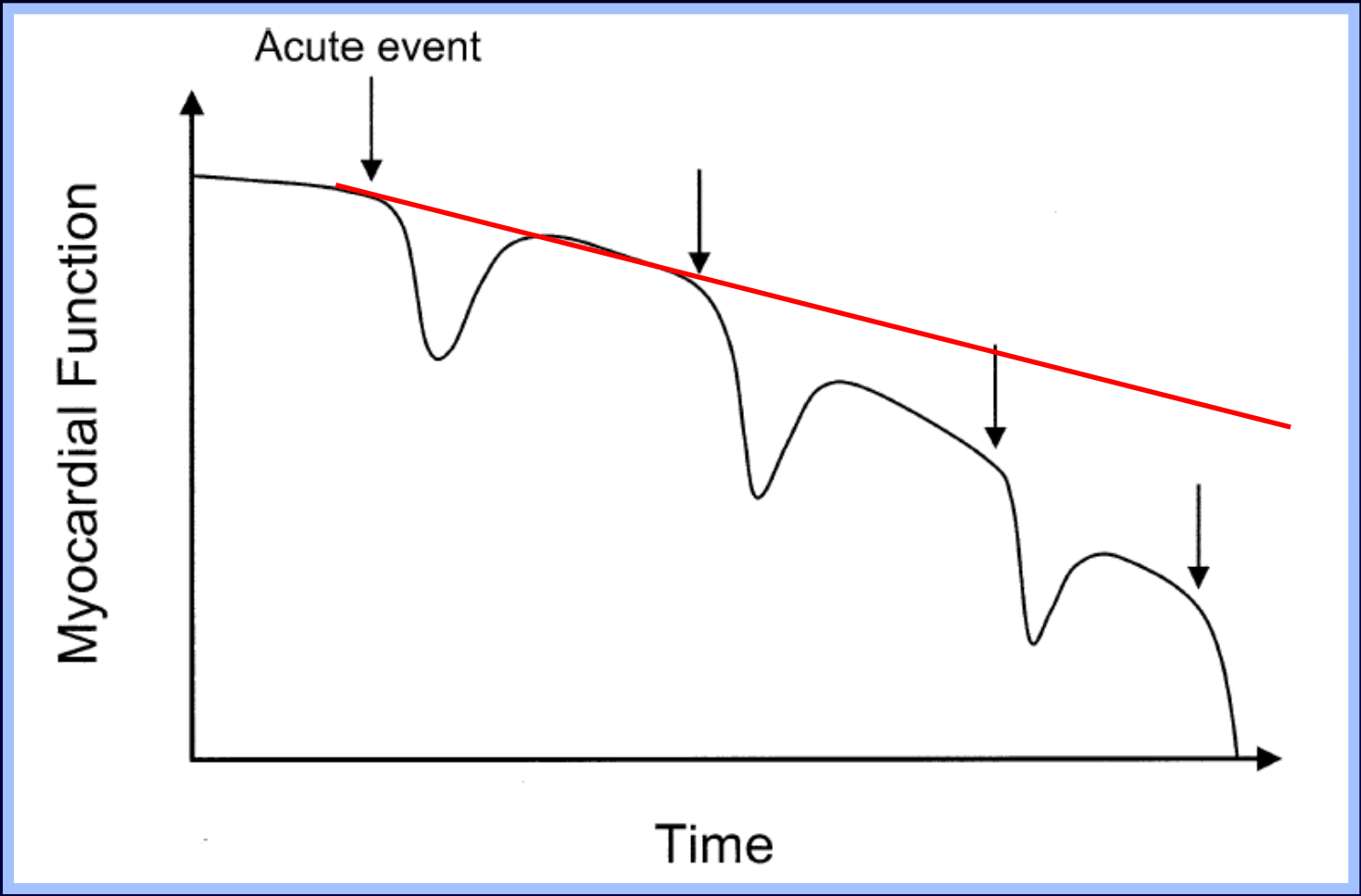


Pepper, Arch Intern Med 1999.

CHF Vicious Cycle (Simplified)



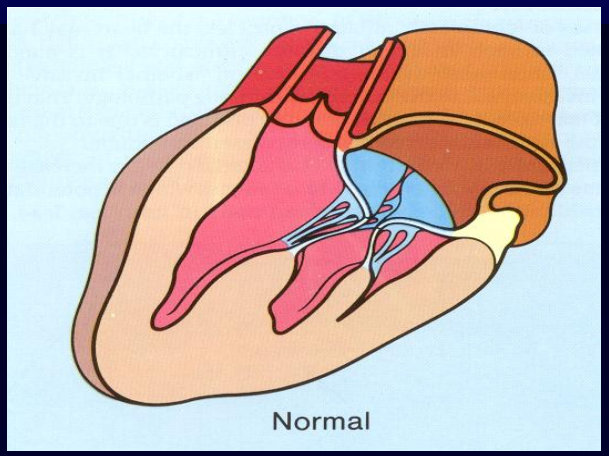
Acute Exacerbations May Contribute to CHF Progression



Gheorghiade M, et al. Am J Cardiol. 2005;96:11G-17G.

Cardiac remodeling

Jessup, Brozena. *NEJM* 2003;348:2007

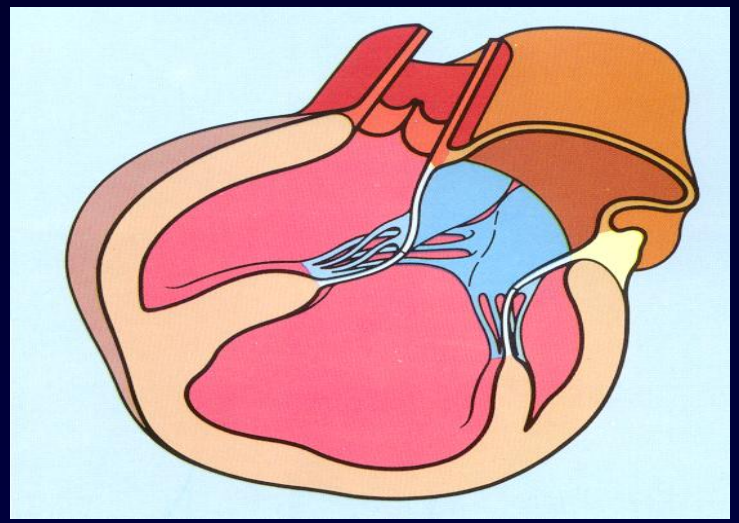


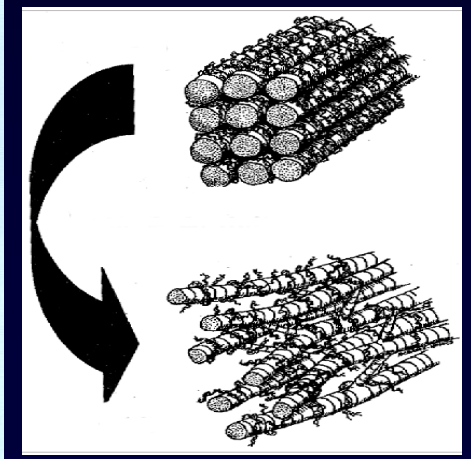
Stage A

Dilated cardiomyopathy

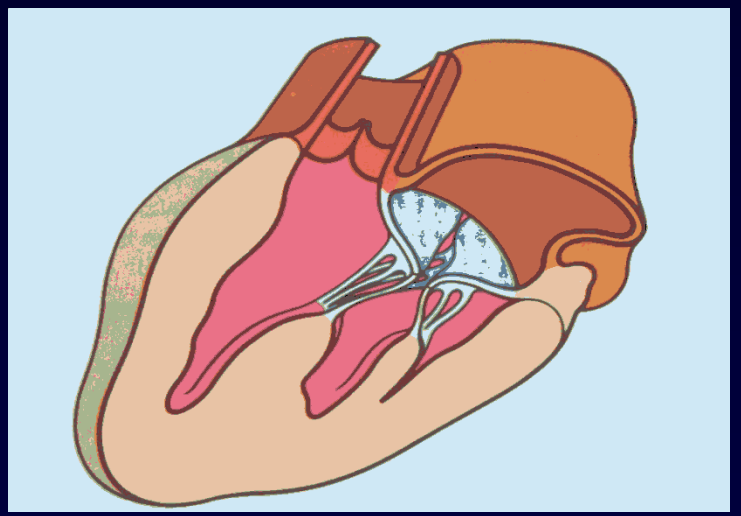
Hypertensive or diabetic heart disease

Stage B,C,D





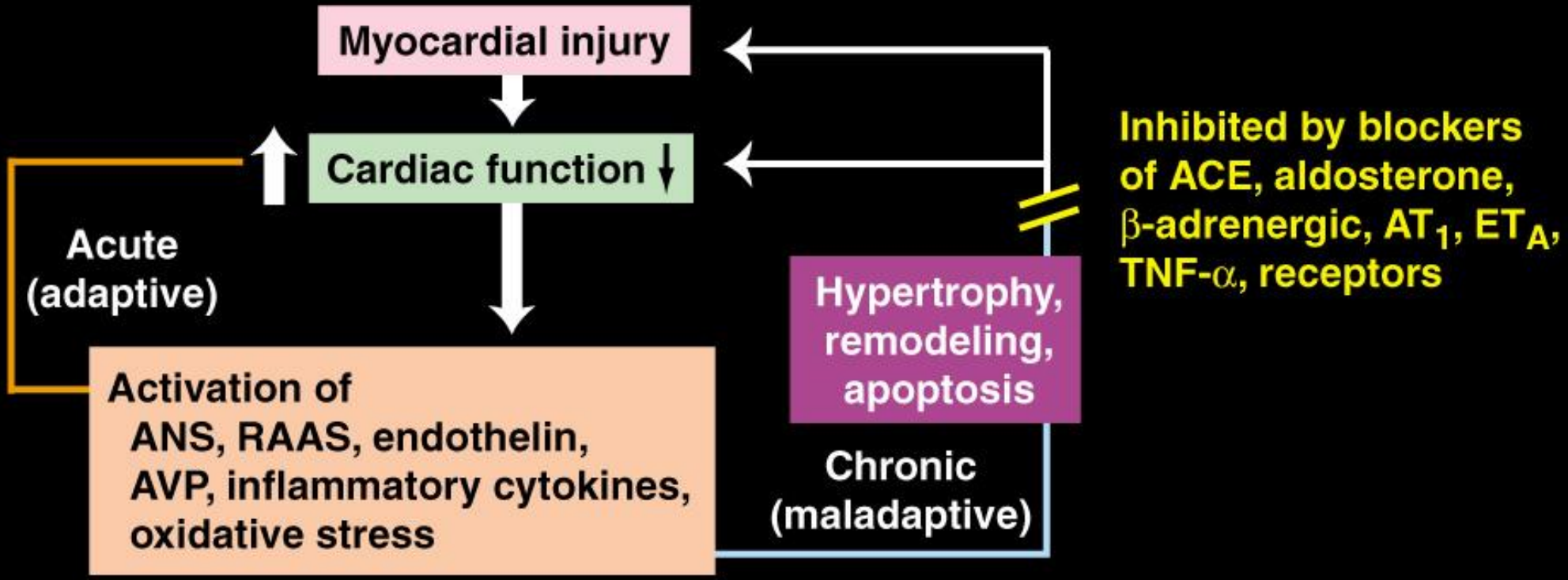
Stage B,C,D



LV dilatation, Globular shape
Systolic LV dysfunction
Mitral regurgitation

Normal cavity size, Concentric LVH
Diastolic dysfunction
Enlarged left atrium

Interplay between cardiac function and neurohormonal system in HF



ANS = adrenergic nervous system
RAAS = renin-angiotensin-aldosterone system
AVP = arginine vasopressin
ET = endothelin

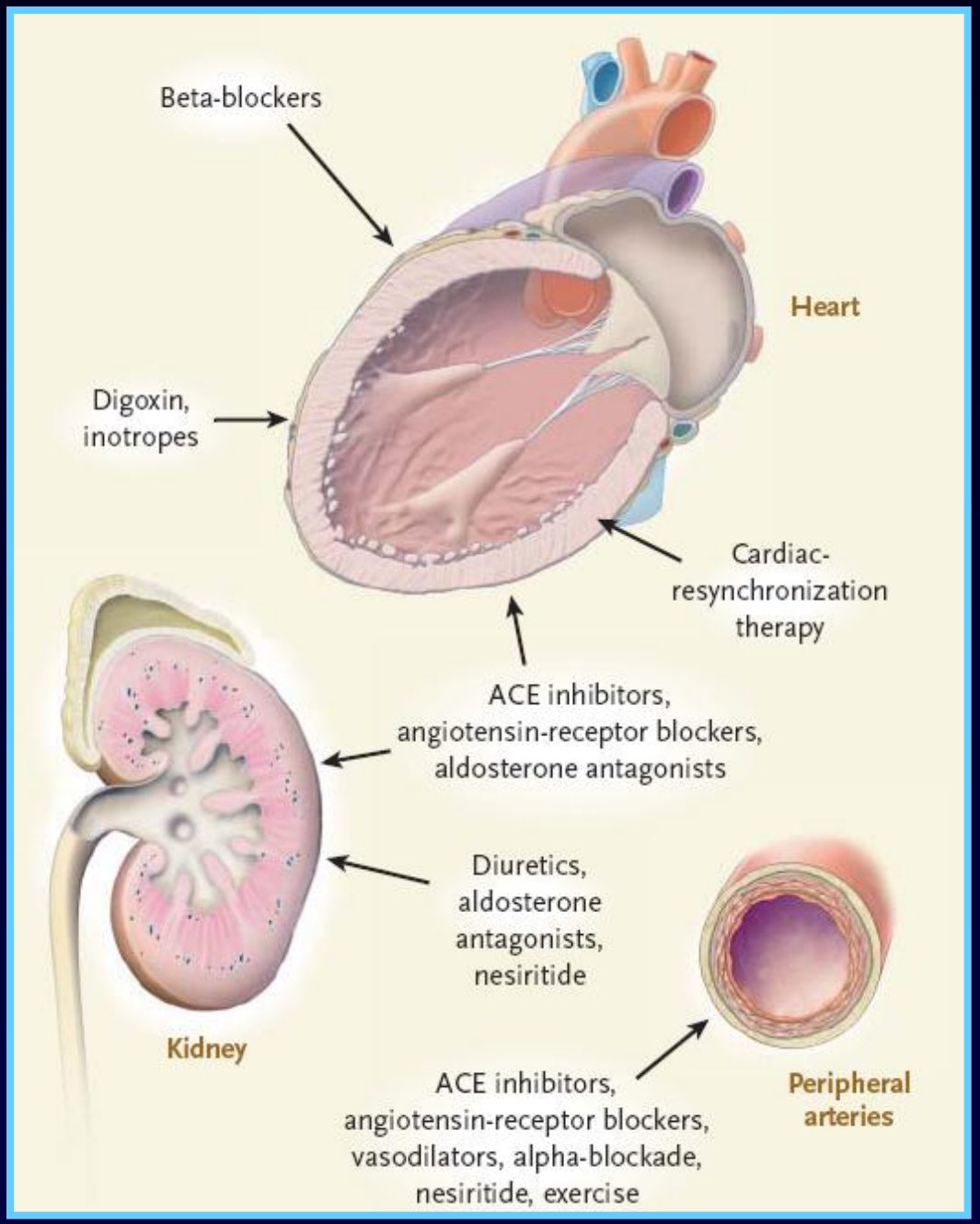
Modified from Braunwauld E, Bristow MR. *Circulation*. 2000;102(suppl):IV-14–IV-23.

만성 심부전의 약물 치료

- Key Drugs
- Key Issues

Congestive Heart Failure

Optimal Medical Treatment is very important !



Current Medical Treatment for Heart Failure

- ACE inhibitors/ARBs
- β - blockers
- Spironolactone

- Diuretics
- Digitalis
- Hydralazine/nitrates
- Others

Current Medical Treatment in the Evolution of Heart Failure

A

- Treat risk factors
- Avoid toxics
- ACEIs or ARBs *in selected pts.*

B

- ACEIs or ARBs
- β - blockers

in selected patients

C

- ACEIs
- β - blockers
- Diuretics

- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates

in selected patients

D

- Palliative therapy
- Mech. Assist device
- Heart Transplant

ACC/AHA HF guidelines 2009

Practical Use of Diuretics

- Optimal use of diuretics is the cornerstone for treatment of HF
- All pts. who have *current* evidence of, and with *prior* history of fluid retention
- Generally, combined with *RAS blockers and β-blockers*, and *moderate dietary sodium restriction(3-4 gm/d)*
- No long-term studies for diuretics effects on morbidity and mortality of HF

Practical Use of β-blockers

Three β-blockers

: effective in mortality reduction in pts. with CHF

1. **Bisoprolol ➔ CIBIS II study**
2. **Metoprolol succinate(sustained release) ➔ MERIT HF study**
3. **Carvedilol ➔ CAPRICORN, US Carvedilol study**

One of these 3 blockers should be given in all pts. with Stage C HF.

Which patients are sufficiently stable to be considered for treatment with a β–blockers ?

1. Not patients in CCU
2. Not patients with volume overload evidence
3. Not patients have required recent treatment with intravenous inotropic agent

Start at very low doses,
followed by gradual increments (2 wks)
to target dose or maximal tolerable dose (?)

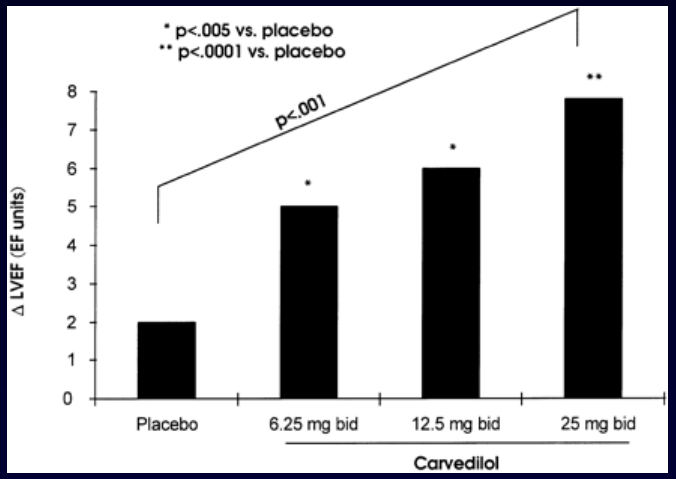
4 types of adverse reactions of β-blockers

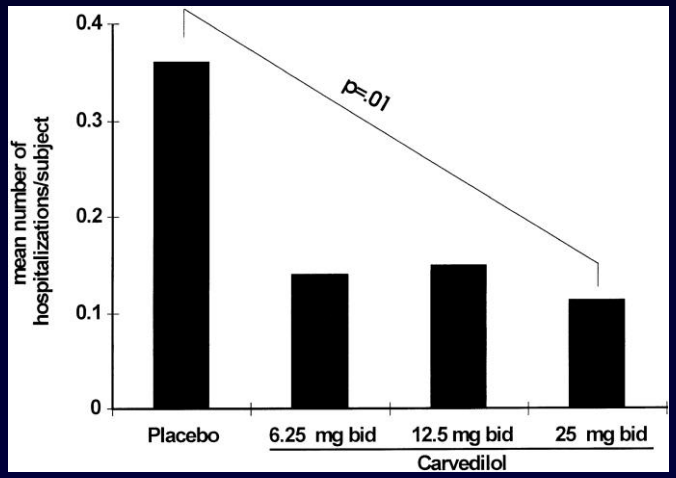
1. Fluid retention and worsening HF
2. Fatigue
3. Bradycadia and heart block
4. Hypotension

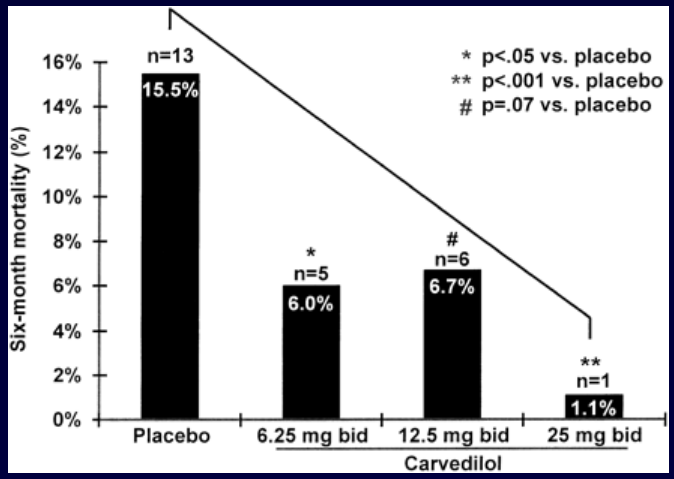
2009 ACC/AHA Guideline

2009 Focused Update Recommendations	Comments
Class I (Continued)	
14. In patients hospitalized with HF with reduced ejection fraction not treated with oral therapies known to improve outcomes, particularly ACE inhibitors or ARBs and beta-blocker therapy, initiation of these therapies is recommended in stable patients prior to hospital discharge.[239,240] *(Level of Evidence: B)*	New recommendation
15. Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents. Beta-blocker therapy should be initiated at a low dose and only in stable patients. Particular caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course.[239,240] *(Level of Evidence: B)*	New recommendation
16. In all patients hospitalized with HF, both with preserved (see Section 4.3.2., Patients With HF and Normal LVEF, in the full-text guideline) and low EF, transition should be made from intravenous to oral diuretic therapy with careful attention to oral diuretic dosing and monitoring of electrolytes. With all medication changes, the patient should be monitored for supine and upright hypotension, worsening renal function and HF signs/symptoms. *(Level of Evidence: C)*	New recommendation
17. Comprehensive written discharge instructions for all patients with a hospitalization for HF and their caregivers is strongly recommended, with special emphasis on the following 6 aspects of care: diet, discharge medications, with a special focus on adherence, persistence, and uptitration to recommended doses of ACE inhibitor/ARB and beta-blocker medication, activity level, follow-up appointments, daily weight monitoring, and what to do if HF symptoms worsen. *(Level of Evidence: C)*	New recommendation
18. Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care for patients hospitalized with HF.[112,241–247] *(Level of Evidence: B)*	New recommendation

Dose-response benefit (MOCHA Study)







Bristow MR, et al. Circulation 1996.

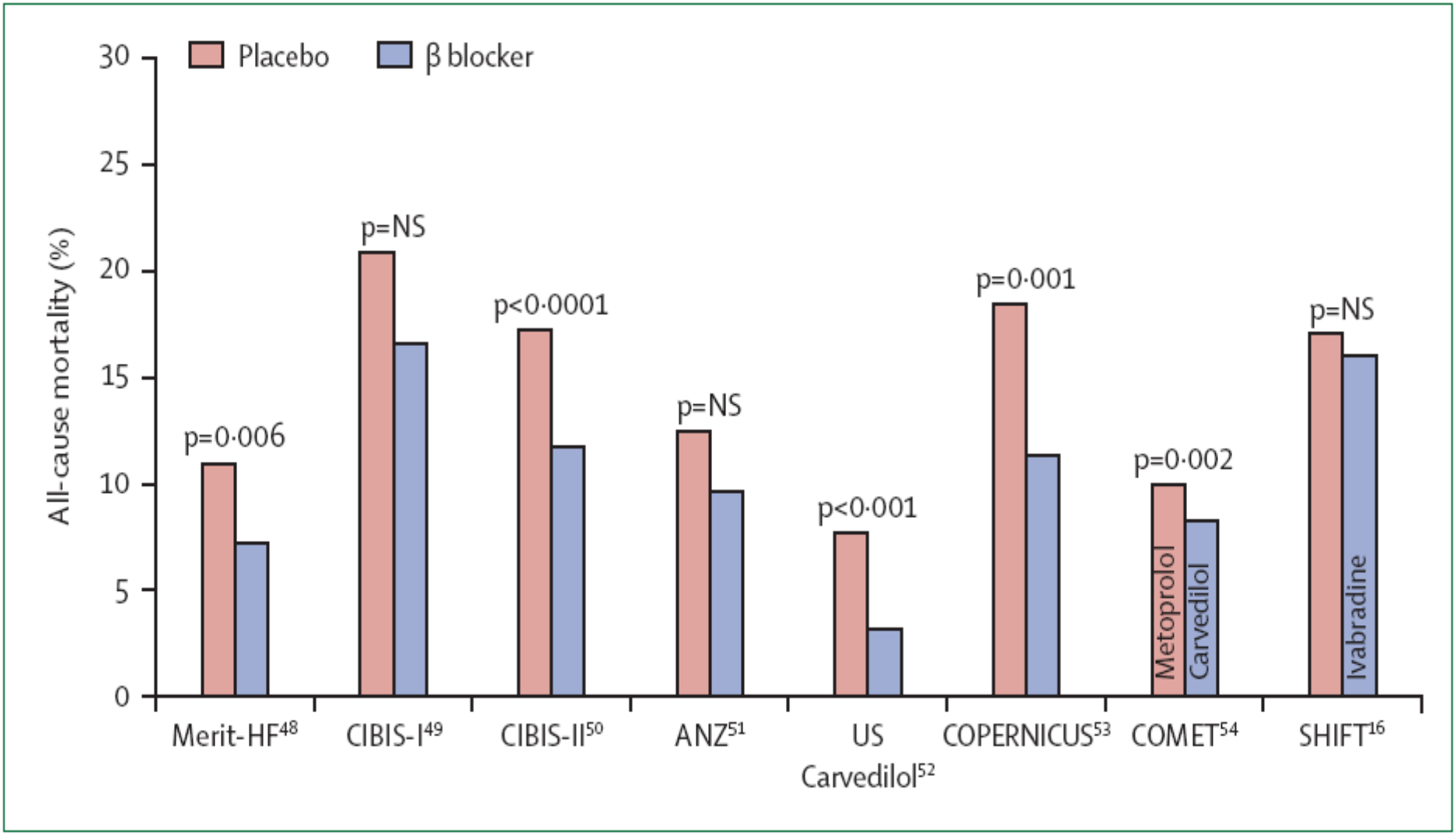


Figure 5: **All-cause mortality in selected chronic heart failure trials**[16,48-54]

Ivabradine is only drug without a demonstrated beneficial effect on mortality. NS=non-significant.

Practical Use of ACEIs

- All pts. with all NYHA classes of HF due to LV dysfunction, unless contraindicaiton to their use.
➔ First choice of drug !

- No differences among available ACEIs on symptoms or survival. (*captopril, enalapril, lisionopril, perindopril, ramipril and trandopril*)

- Should be initiated with lose doses, until maximal dose.

- Abrupt withdrawal of ACEIs can lead to clinical deterioration of HF and should be avoided.

Dose-response benefit ? (ATLAS Study)

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

Background—Angiotensin-converting enzyme (ACE) inhibitors are generally prescribed by physicians in doses lower than the large doses that have been shown to reduce morbidity and mortality in patients with heart failure. It is unclear, however, if low doses and high doses of ACE inhibitors have similar benefits.

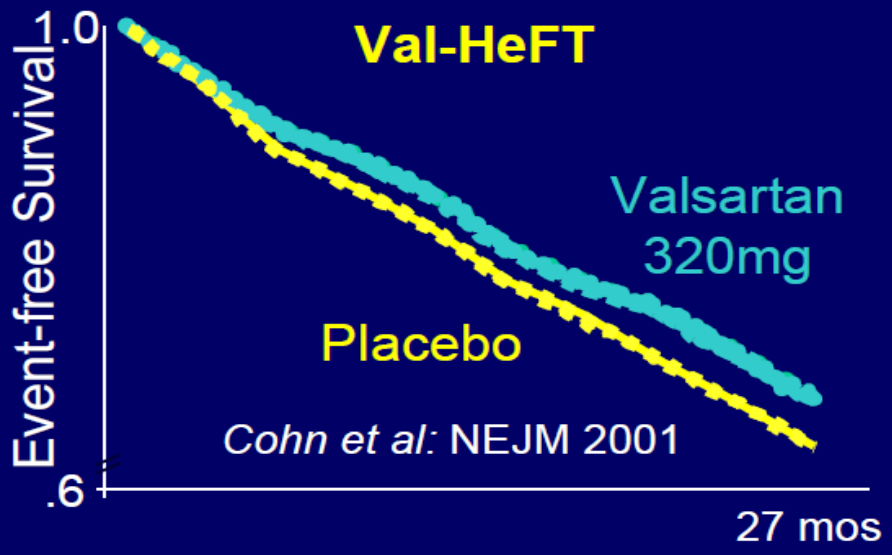
Methods and Results—We randomly assigned 3164 patients with New York Heart Association class II to IV heart failure and an ejection fraction ≤30% to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n=1596) or high doses (32.5 to 35 mg daily, n=1568) of the ACE inhibitor, lisinopril, for 39 to 58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death (P=0.128) but a significant 12% lower risk of death or hospitalization for any reason (P=0.002) and 24% fewer hospitalizations for heart failure (P=0.002). Dizziness and renal insufficiency was observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.

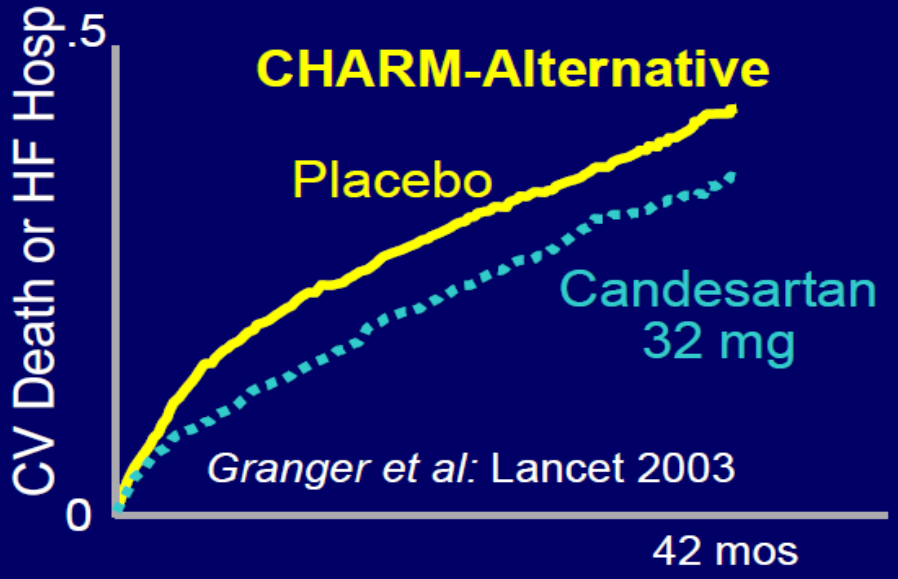
Conclusions—These findings indicate that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small. (***Circulation.*** **1999;100:2312-2318.)**

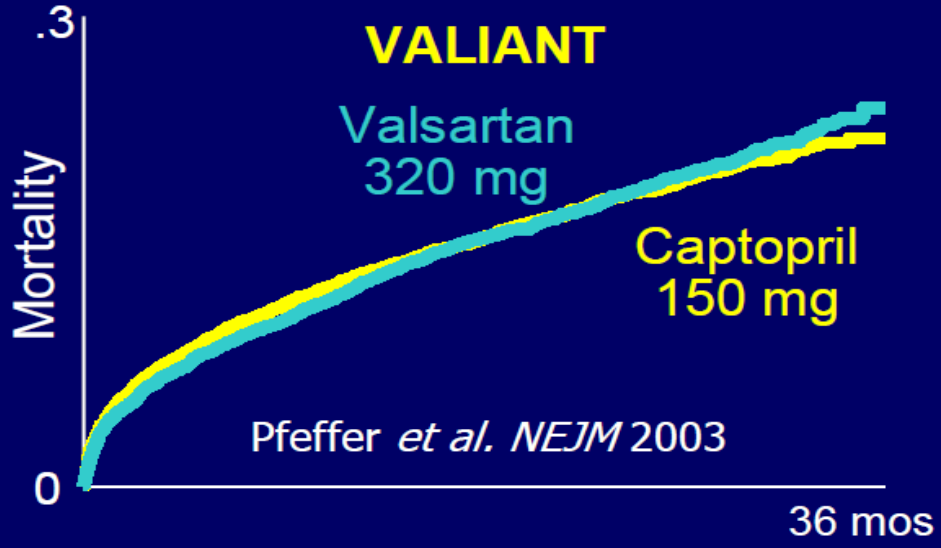
Practical Use of ARBs

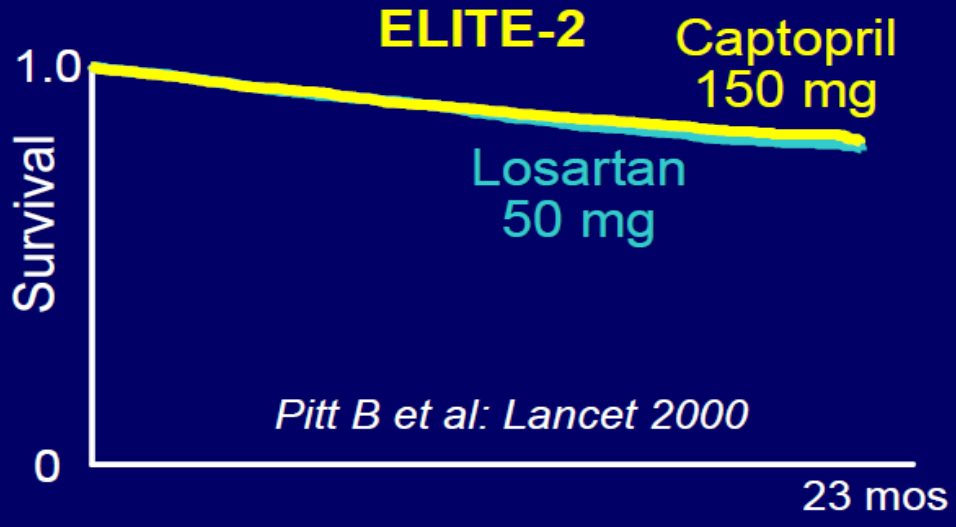
- Consider ACEI-intolerant HF patients.
- Benefit in morbidity and mortality-but not mortality alone, reasonable alternative, compared with ACEIs, (Valsartan, Candesartan).
- Less frequent angioedema.
- Addition of an ARB to an ACEI (CHARM-added & Val-HeFT)➔ reduce hospitalization, but controversy for all-cause mortality reduction

ARBs in Heart Failure









Higher Doses of Losartan are More Effective ?

ELITE II
mean dose: 41 mg

OPTIMAAL
mean dose:
45 mg

RENAAL
mean dose: 86 mg

LIFE
mean dose:
82 mg

HEAAL
losartan 50 mg
vs. 150 mg

Negative

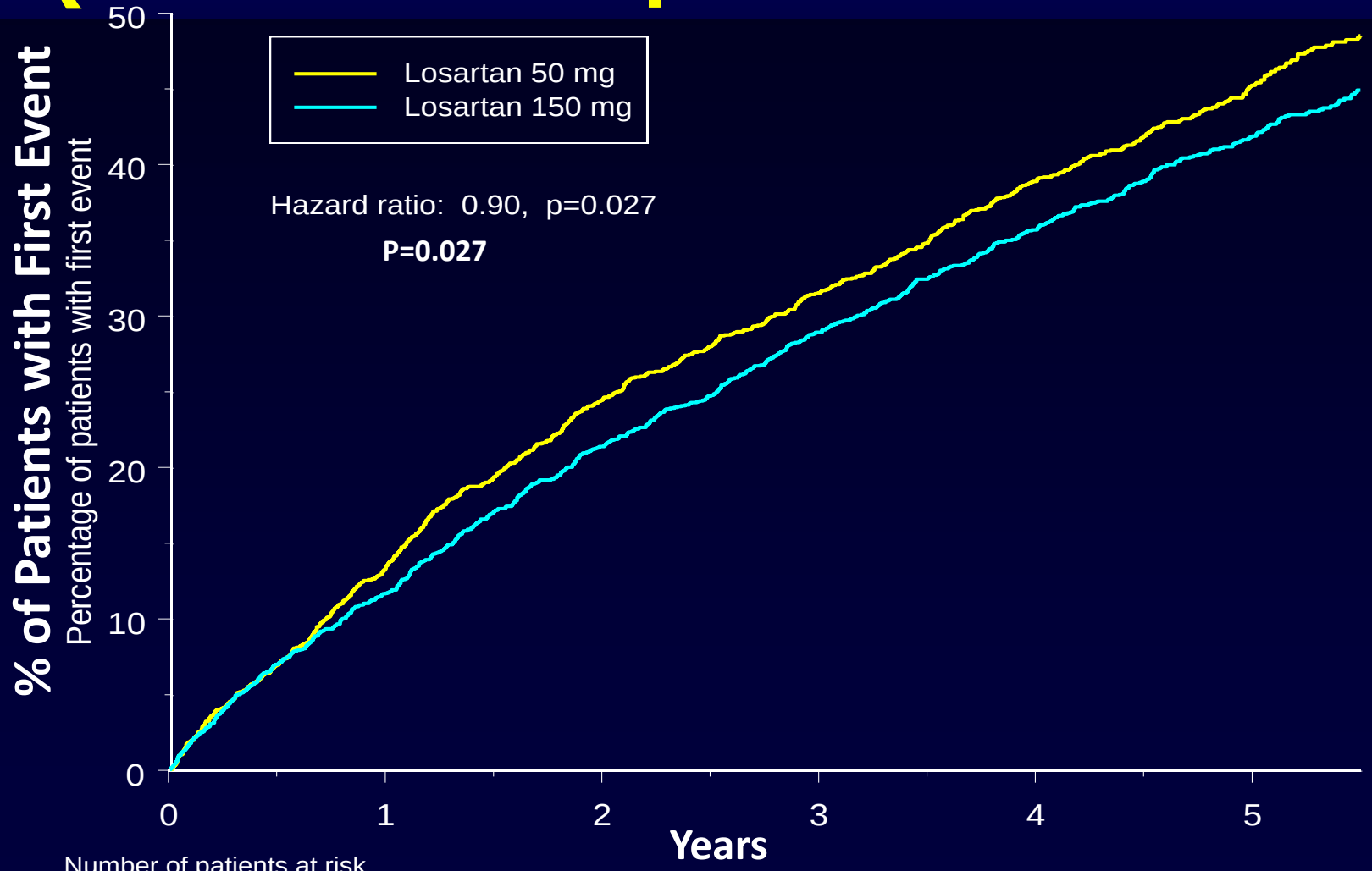
Lancet 2000; 355:1582-87
Lancet 2002; 360: 752-60

Positive

N Engl J Med 2001; 345:861-69
Lancet 2002; 359:995-1003

Lancet 2009; 374: 1840–48

HEAAL Study (Death or Hospitalization for HF)



Number of patients at risk					
Losartan 50 mg	1646	1422	1277	1126	644
Losartan 150 mg	1684	1493	1344	1205	711

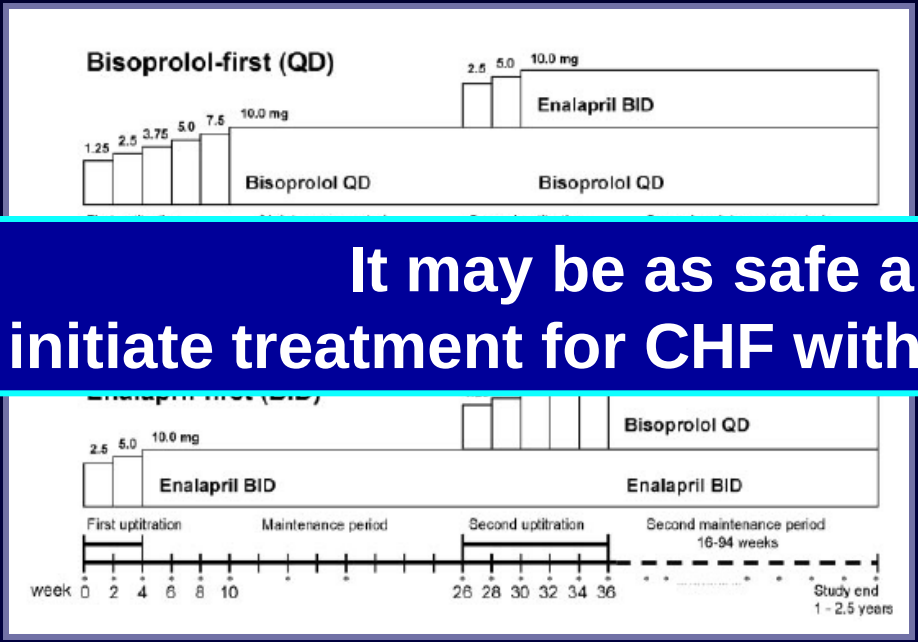
ACEI/ARB or Beta blockers ?

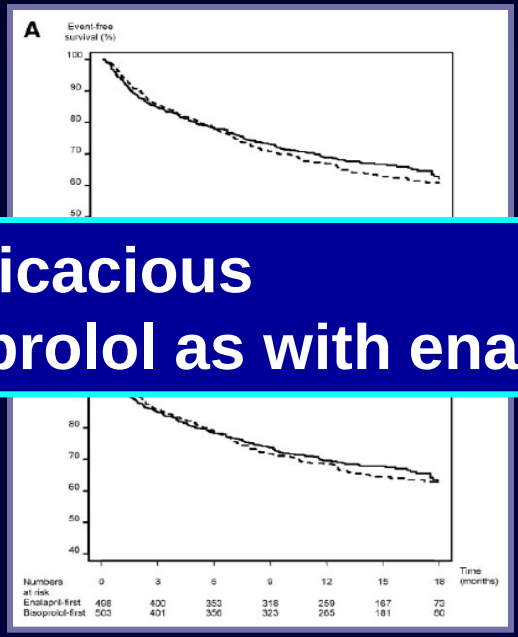
Who is first ?

Inhibit cardiac remodeling

Antiarrhythmic effect

CIBIS III trial





It may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril.

Willenheimer R, et al. Circulation 2005

Practical Use of Aldosterone antagonist

- Add low dose aldosterone antagonist should be considered in carefully pts. with mild to severe HF (EF ≤ 35%, NYHA II-IV) or pts. with LV dysfunction early after MI.

- Should not be given when renal clearance is less than 30 mL per minute. (Cr >2.5 or K^+ >5.0)➔ Hyperkalemia !
- f/u lab : within 72hr, 1 wk, 1 M, 3 M, q 3 M

- *RALE study* : 30 % RRR of mortality, 35% RRR of HF hospitalization over 2 yrs in low doses of spironolactone(12.5 – 25 mg/d) were added to ACEI therapy in HF.
- *EPHESUS study*

: selective aldosterone antagonist, eplerenone , Post-MI HF patients

Hyperkalemia Risk Groups

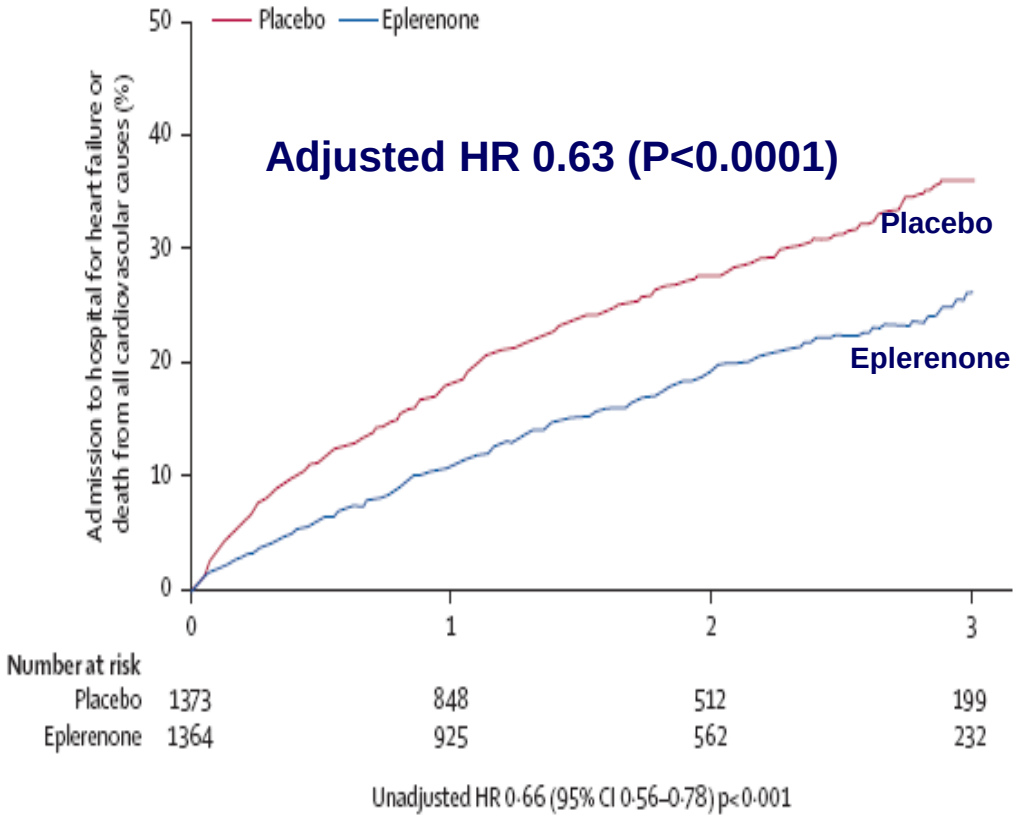
- Elderly
- DM w/ renal disease
- NSAID
- Low furosemide requirement

If dehydration, vomiting, diarrhea, recommend careful monitoring K+ level !

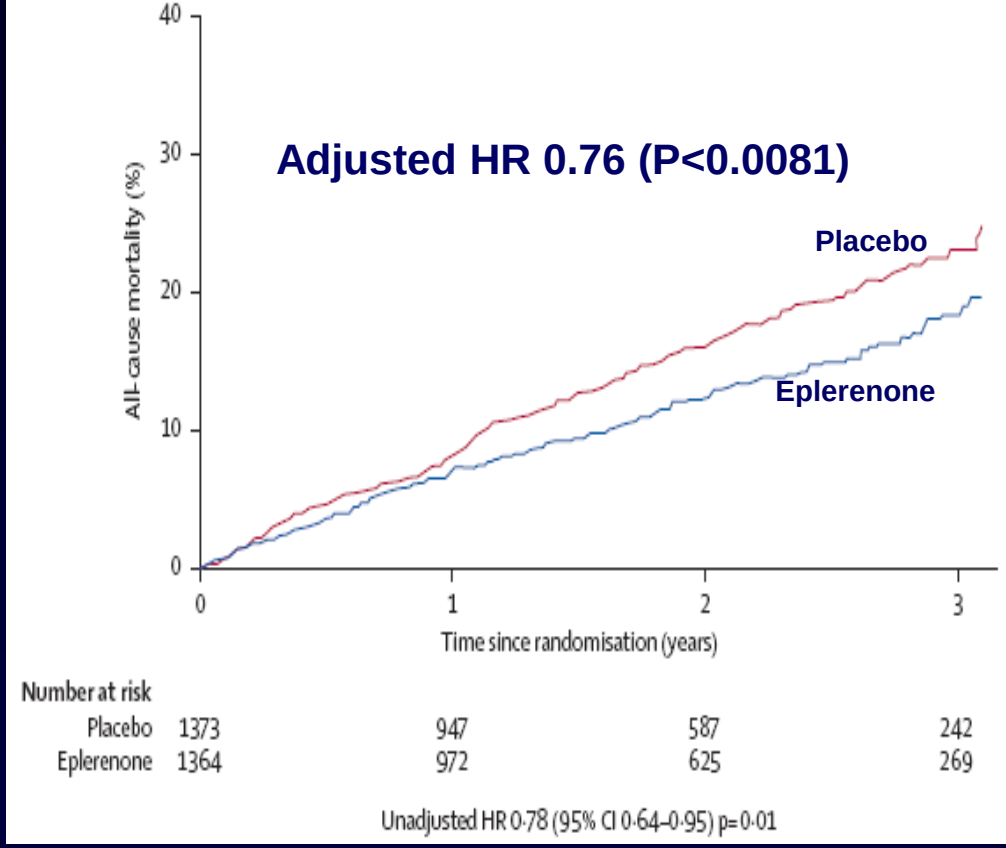
EMPHASIS-HF

NYHA II CHF, EF ≤ 35 %, eplerenon (up to 50 mg/d)

CV Death



All-cause Death



Zannad F, et al. N Engl J Med 2011.

Practical Use of Digoxin

- Benefit for V. rate control in pts with HF and A. fib
- Consider adding in symptomatic pts. with NSR during therapy with diuretics, an ACEI and *β-blocker.*
- No effect on mortality reduction and asymptomatic HF pts. with NSR
- More than 1.0 ng/ml → deleterious CV effect in long-term

Class I drug (2001) → Class IIa drug (2005)

HF with renal insufficiency

6.2.1. Patients With Renal Insufficiency

Patients with HF frequently have impaired renal function as a result of poor renal perfusion, intrinsic renal disease, or drugs used to treat HF. Patients with renal hypoperfusion or intrinsic renal disease show an impaired response to diuretics and ACEIs[275,751] and are at increased risk of adverse effects during treatment with digitalis.[370] Renal function may worsen during treatment with diuretics or ACEIs,[274,527] although the changes produced by these drugs are frequently short-lived, generally asymptomatic, and reversible. Persistent or progressive renal functional impairment often reflects deterioration of the underlying renal disease process and is associated with a poor prognosis.[41,752] The symptoms of HF in patients with end-stage renal disease may be exacerbated by an increase in loading conditions produced both by anemia[753] and by fistulas implanted to permit dialysis. In addition, toxic metabolites and abnormalities of phosphate, thyroid, and parathyroid metabolism associated with chronic renal insufficiency can depress myocardial function.

Despite the potential for these adverse interactions, most patients with HF tolerate mild to moderate degrees of functional renal impairment without difficulty. In these individuals, changes in blood urea nitrogen and serum creatinine are generally clinically insignificant and can usually be managed without the withdrawal of drugs needed to slow the progression of HF. However, if the serum creatinine increases to more than 3 mg per dL, the presence of renal insufficiency can severely limit the efficacy and enhance the toxicity of established treatments.[275,370,751] In patients with a serum creatinine greater than 5 mg per dL, hemofiltration or dialysis may be needed to control fluid retention, minimize the risk of uremia, and allow the patient to respond to and tolerate the drugs routinely used for the management of HF.[548,754]

SCr > 3.0 mg/dL 일 때는,
심부전 약물 치료 효과를 방해하고 부작용을 일으킬 확률이 높으므로 주의를 요한다.

ACC/AHA HF guidelines 2009

COPD in HF patients

- COPD is an independent risk factor of mortality and CV morbidity in HF

ACEIs and Beta-blockers ?

6.2.2. Patients With Pulmonary Disease

Because dyspnea is the key symptom in both HF and pulmonary disease, it is important to distinguish the 2 diseases and to quantify the relative contribution of cardiac and pulmonary components to the disability of the patient when these disorders coexist. Exercise testing with simultaneous gas exchange or blood gas measurements may be helpful in this regard, particularly when used in conjunction with right heart catheterization.[755]

Some drugs used to treat HF can produce or exacerbate pulmonary symptoms. Angiotensin converting enzyme inhibitors can cause a persistent nonproductive cough that can be confused with a respiratory infection, and conversely, ACEIs may be inappropriately stopped in patients with pulmonary causes of cough. Therefore, physicians should seek a pulmonary cause in all patients with HF who complain of cough, whether or not they are taking an ACEI. The cough should be attributed to the ACEI only if respiratory disorders have been excluded and the cough disappears after cessation of ACEI therapy and recurs after reinstitution of treatment. Because the ACEI-related cough does not represent any serious pathology, many patients can be encouraged to tolerate it in view of the important beneficial effects of ACEIs.

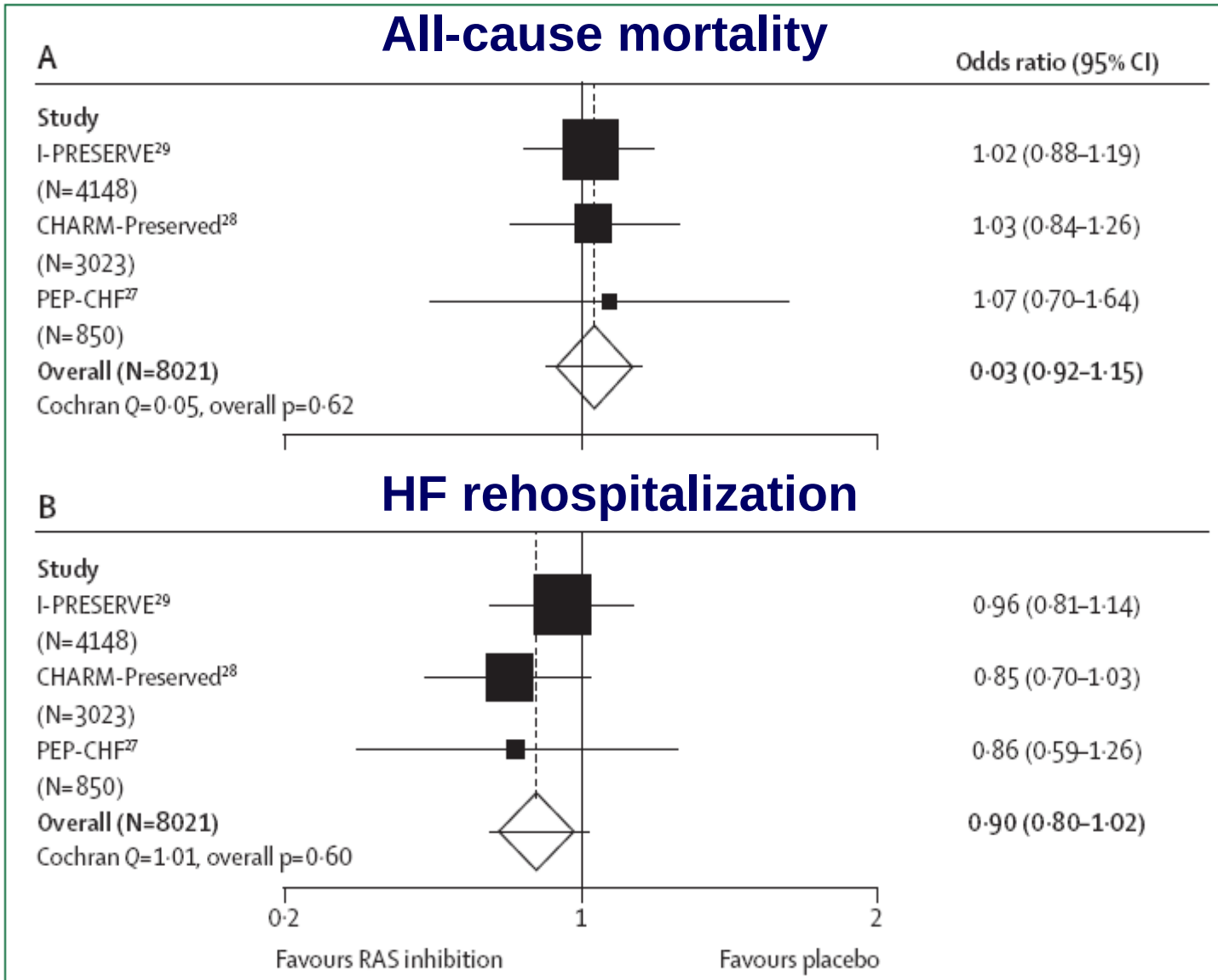
Beta blockers can aggravate bronchospastic symptoms in patients with asthma; however, many patients with asymptomatic or mild reactive airways disease tolerate beta-blockers well. Also, most patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain reasonable candidates for beta-blockade.[756] Of note, both metoprolol tartrate and bisoprolol may lose their beta-1 selectivity when prescribed in doses that have been associated with an improvement in survival in patients with HF.

Recommend Beta-1 selective blockers in all pts with COPD + CHF
Avoid during exacerbation of COPD and bronchospasm

Clinical trials in HF-PSF

Trial	End Points	Outcomes
CHARM-Preserved	CV death & hospitalisation	No difference in death. Candesartan reduced hospitalisation
I-PRESERVE	Mortality & hospitalisation	No differences in all cause mortality and CV hospitalization
PEP-CHF	All-cause mortality and CV hospitalisation	Reduced mortality and CV hospitalisation vs. placebo at 1 yr
TOPCAT	All-cause mortality and CV hospitalisation	Not yet reported
SENIORS	All-cause mortality and CV hospitalisation	Reduced mortality and CV hospitalisation in 10mg dose group vs. placebo
beta-PRESERVE	Hospitalization for heart failure and CV death	Not yet reported

All-cause mortality



HF rehospitalization

Shah RV, et al. J Card Fail 2010

ESC guidelines on management of HF-PEF

- No treatment has official indication to date
- Therapeutic guidelines of the ESC:
  - Diuretics : control sodium and water retention and releive breathlessness and edema
  - Control HTN and myocardial ischemia
  - Control ventricular rate in AF
  - Verapamil : may improve exercise capacity and Sx in small studies

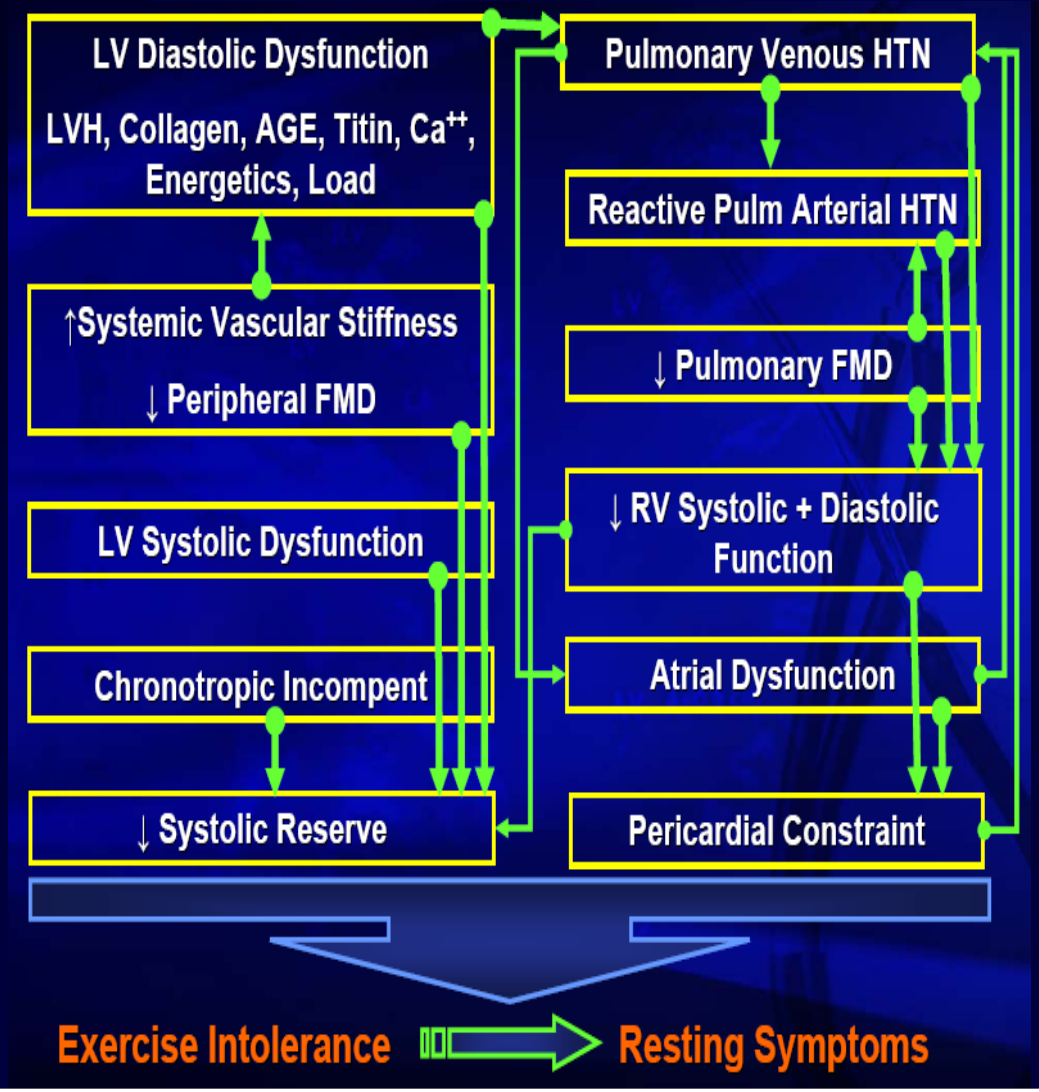
HF w/ PEF

Table 8. Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Physicians might recommend coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure might be considered.	IIb	C

ACC/AHA HF guidelines 2009

수축기 기능이 유지된 심부전 환자의 치료?



"In order for this field to move forward, a better understanding of the (clinical heterogeneity and) mechanisms underlying this syndrome and the potential targets for treatment is required."

New directions in the medical treatment of HF

Neurohormonal blockade

- **Oral renin inhibitor**

: ALOFT, ASPIRE, ASTRONAUT ATMOSPHERE study..

- **Omapatrilat**

: vasopeptidase inhibitor, angio-edema(+)

- **LCZ696**

: AR-neprilysin inhibitor, angio-edema(-)
PARADIGM-HF study

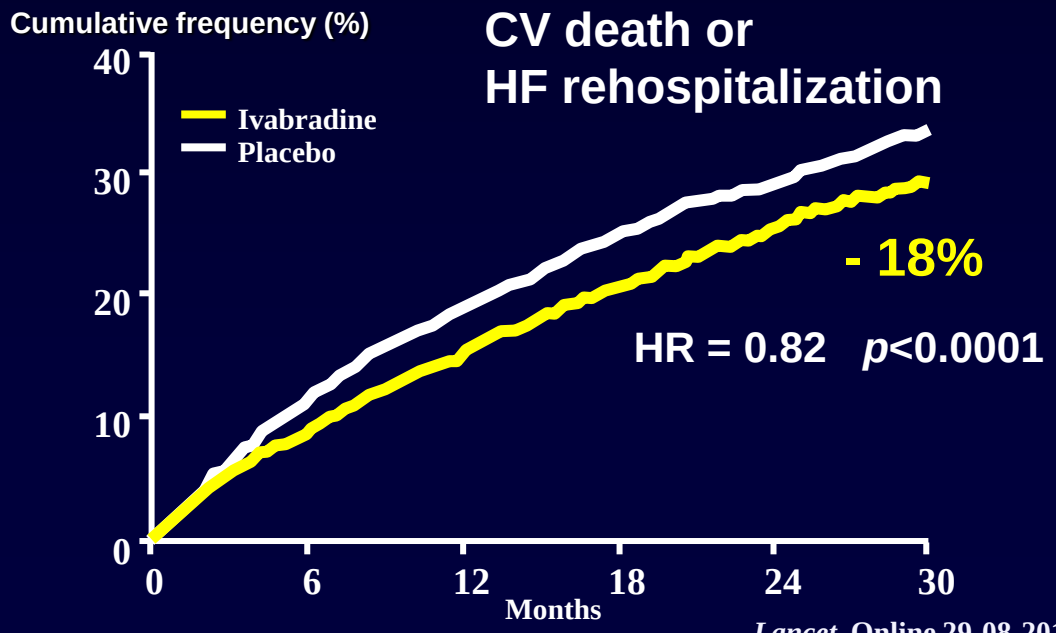
- **Vaptan**

: vasopressin antagonist
EVEREST study

Heart rate reduction

SHIFT

Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial



Lancet. Online 29-08-2010

Epilogue

" The management of HF should be aimed at preventing or delay the progression of left ventricular dysfunction *by understanding pathophysiology of HF*, no longer be confined to the relief of symptoms "

Appreciate Your Attention !!