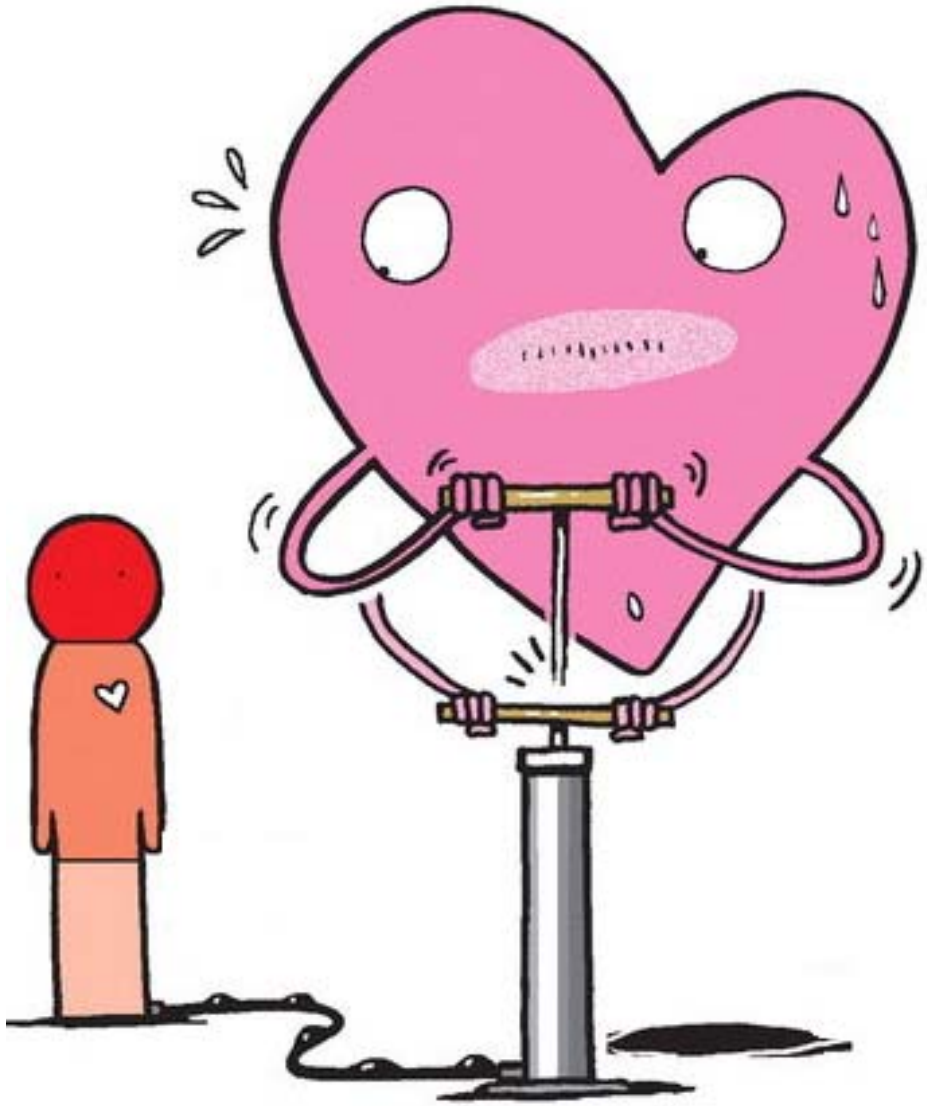
Update on the Treatment of Chronic Heart Failure 2012

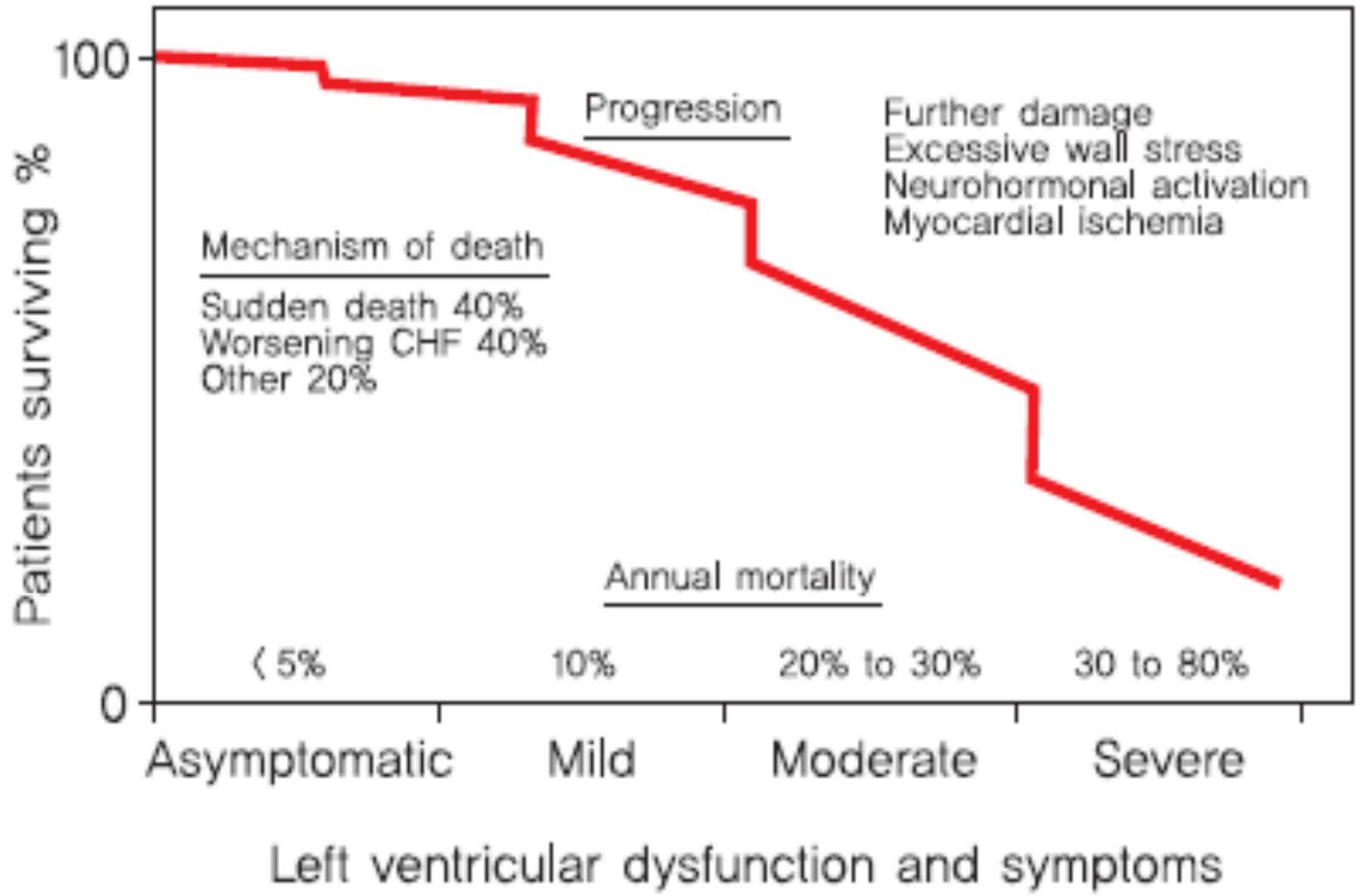
Antialdosterone treatment in heart failure

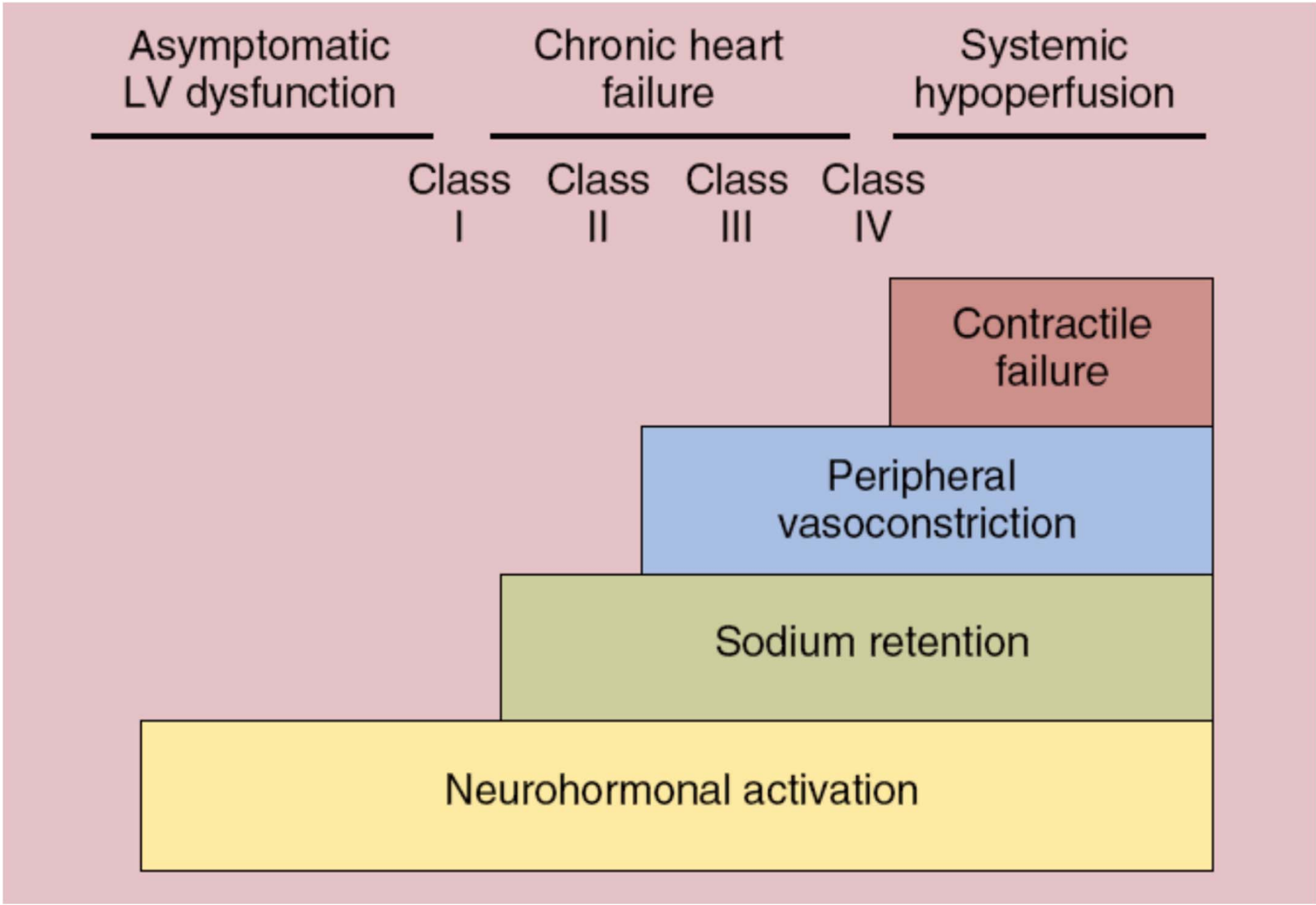
전남의대
윤현주

Chronic Heart Failure



Prognosis of Heart failure





Cecil, Text book of Internal Medicine, 22th edition

Classification of Heart Failure

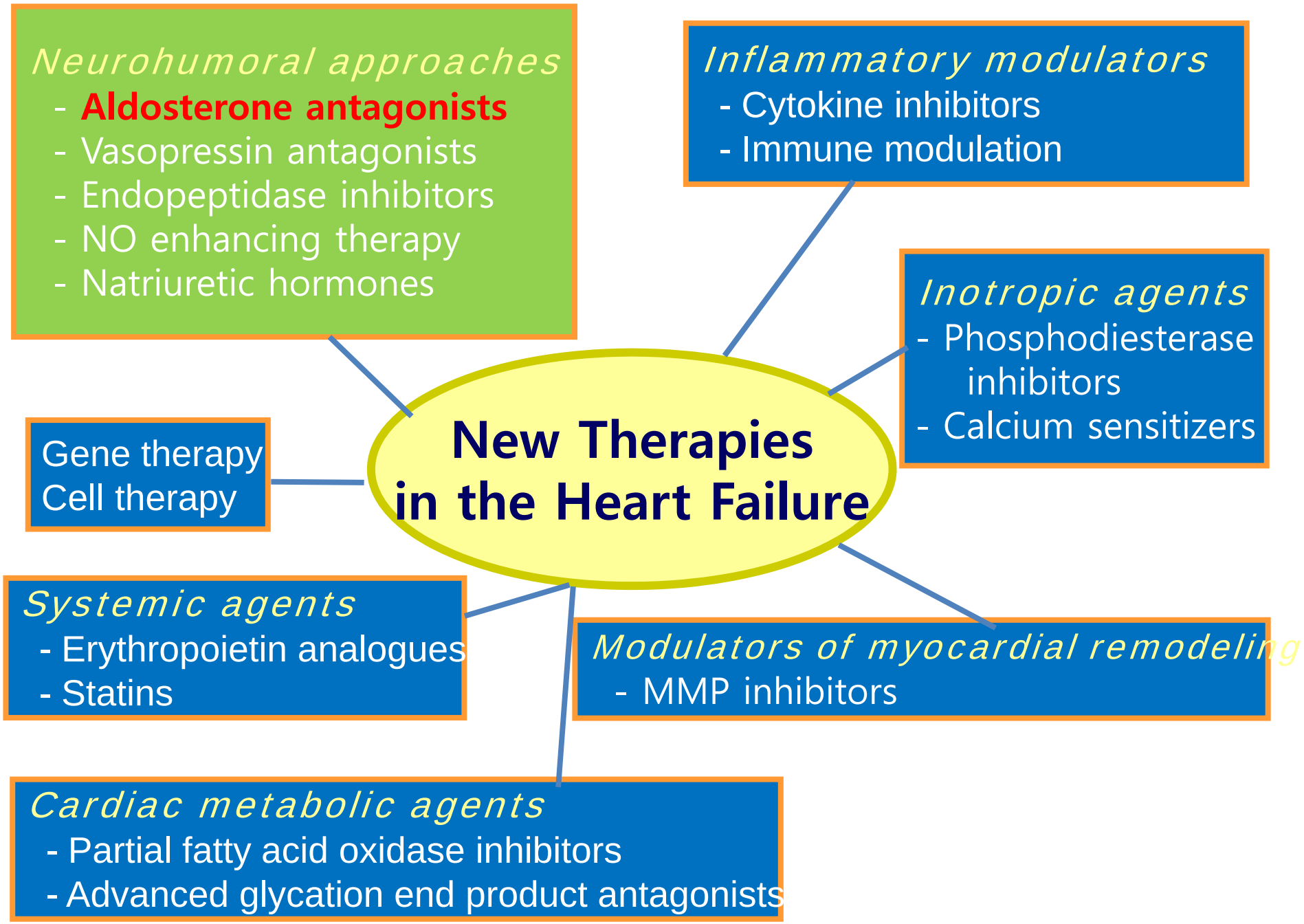
	Stage	Patient Description
A	High risk for developing heart failure (HF)	• Hypertension • CAD • Diabetes mellitus • Family history of cardiomyopathy
B	Asymptomatic HF	• Previous MI • LV systolic dysfunction • Asymptomatic valvular disease
C	Symptomatic HF	• Known structural heart disease • Shortness of breath and fatigue • Reduced exercise tolerance
D	Refractory end-stage HF	• Marked symptoms at rest despite maximal medical therapy (recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Treatment of heart failure

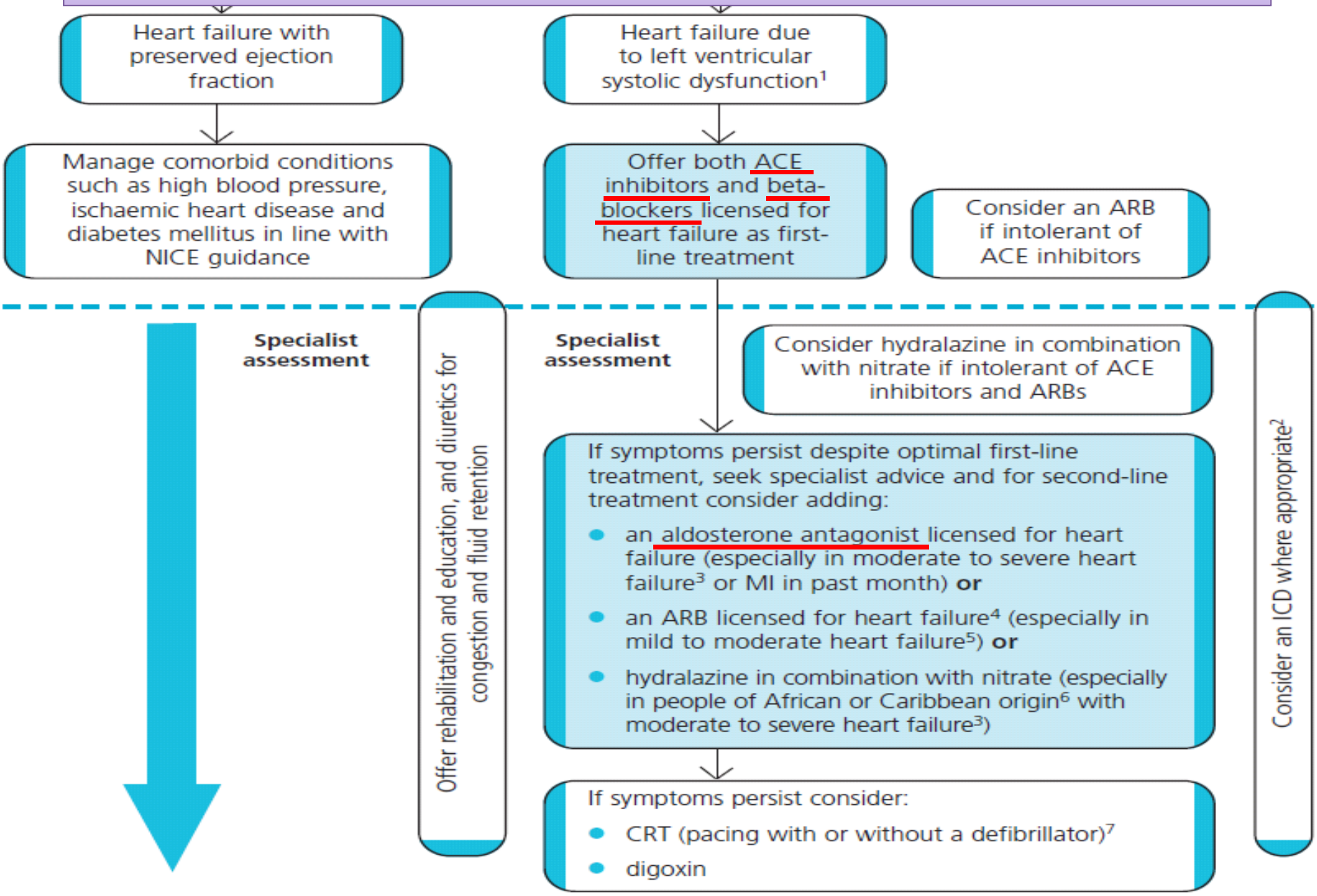
- **Manage other risk factors**
- **Manage coexisting coronary heart disease**
- **Avoid aggravating factors**
  - Non-steroidal anti-inflammatory drugs
  - Short-acting calcium-channel blockers
  - Advise low salt diet
  - Advise a moderate alcohol intake
  - Limiting fluid intake may be appropriate in advanced heart failure, but care is needed to avoid dehydration.
- **Vaccinate people against influenza annually and pneumococcus as a one-off,** as they are at increased risk of infective complications.
- **Consider cardiac rehabilitation, palliative care, and long-term social support** if appropriate.

Treatment of Heart Failure

Stage A	Stage B	Stage C	Stage D
High risk for HF without disease	Structural heart ds without HF signs or symptoms	Structural hearts ds with prior or concurrent signs, symptoms of HF	Refractory HF requiring specialized Tx
Goals 고혈압, 치료, 금연, 이상지질 치료, 정기적 운동, 음주, 약물의 절제, 대사 증후군 조절 **Drugs** ACEI or ARB in appropriate pts	**Goals** Stage A의 모든 것 **Drugs** ACEI or ARB in appropriate pts β-blokers in appropriate pts	**Goals** Stage A의 모든 것, 식이염분 제한 **Drugs for routine use** Diuretics for fluid retention ACEI, β-blokers **Drugs for selected pts** Aldosterone antagonists ARB, Digoxin Hydralazine/nitrates **Devices for selected pts** Biventricular pacing Implantale defibrillator	**Goals** Stage A, B, C의 모든 것 적정 치료 수준 결정 **Options** End-of-life care Extraordinary Mx heart transplant chronic inotrope permanent mechanical support experimental surgery or drugs


Neurohumoral approaches
- Aldosterone antagonists
- Vasopressin antagonists
- Endopeptidase inhibitors
- NO enhancing therapy
- Natriuretic hormones
Inflammatory modulators
- Cytokine inhibitors
- Immune modulation
Inotropic agents
- Phosphodiesterase inhibitors
- Calcium sensitizers
Gene therapy
Cell therapy
New Therapies in the Heart Failure
Systemic agents
- Erythropoietin analogues
- Statins
Modulators of myocardial remodeling
- MMP inhibitors
Cardiac metabolic agents
- Partial fatty acid oxidase inhibitors
- Advanced glycation end product antagonists

Treatment of Heaet Failure



First-line treatment for LVSD

- Offer both ACE inhibitors and beta-blockers licensed for heart failure to all patients with LVSD

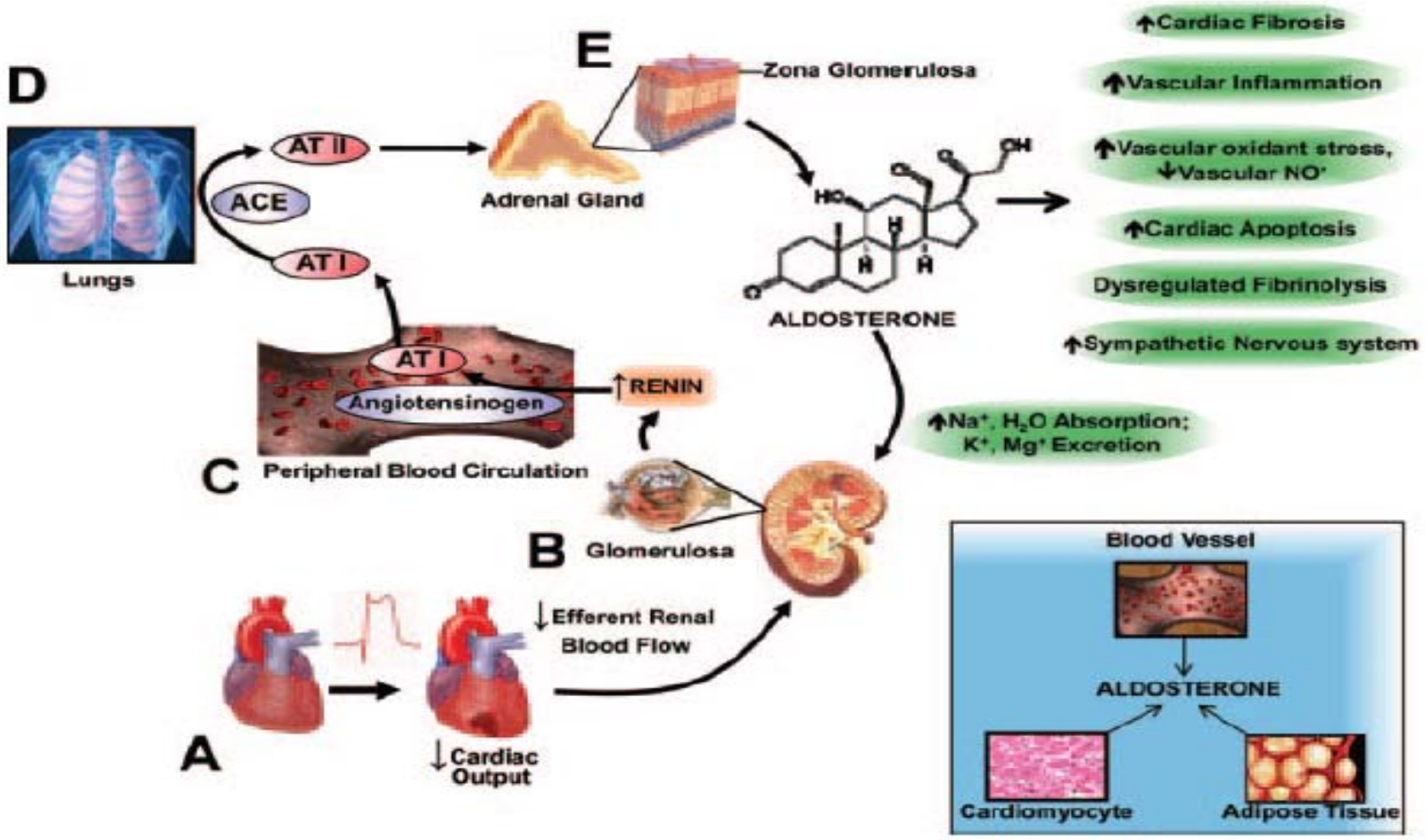
Second-line treatment for LVSD

- aldosterone antagonist licensed for heart failure (especially in NYHA class III–IV or MI in past month)
- ARB licensed for heart failure (especially in NYHA class II-III)
- hydralazine in combination with nitrate (especially in people of African or Caribbean origin with NYHA class III-IV)

Cardiovascular Actions of Aldosterone

- Intravascular fluid retention, volume overload
- Endothelial dysfunction
  -> impaired vascular reactivity
  -> decrease vascular antioxidant capacity,
  increase oxidant stress
  -> limiting bioavailabe nitric oxide
- Activate inflammation
- Alter fibrinolysis
  (increasing PAI-1 expression,
  -> promote tissue fibrosis)

The effect of impaired LV function on aldosterone synthesis



Circulation. 2010;121:934-939

Aldosterone Antagonist

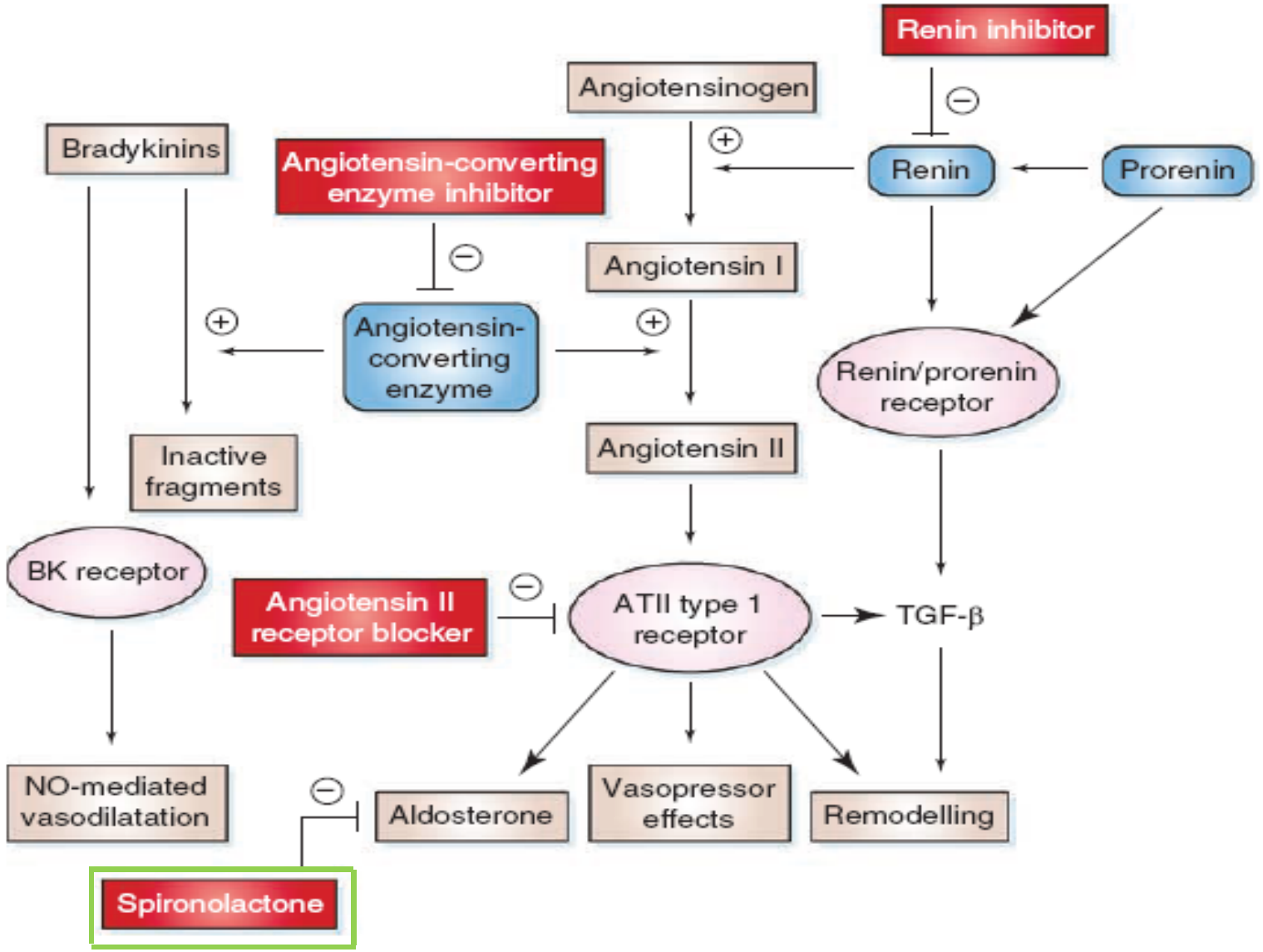
- Potassium sparing diuretics

- Antagonize the effects of aldosterone at the late distal tubule and cortical collecting tubule

- Direct pharmacoligic antagonism of mineralocorticoid receptors

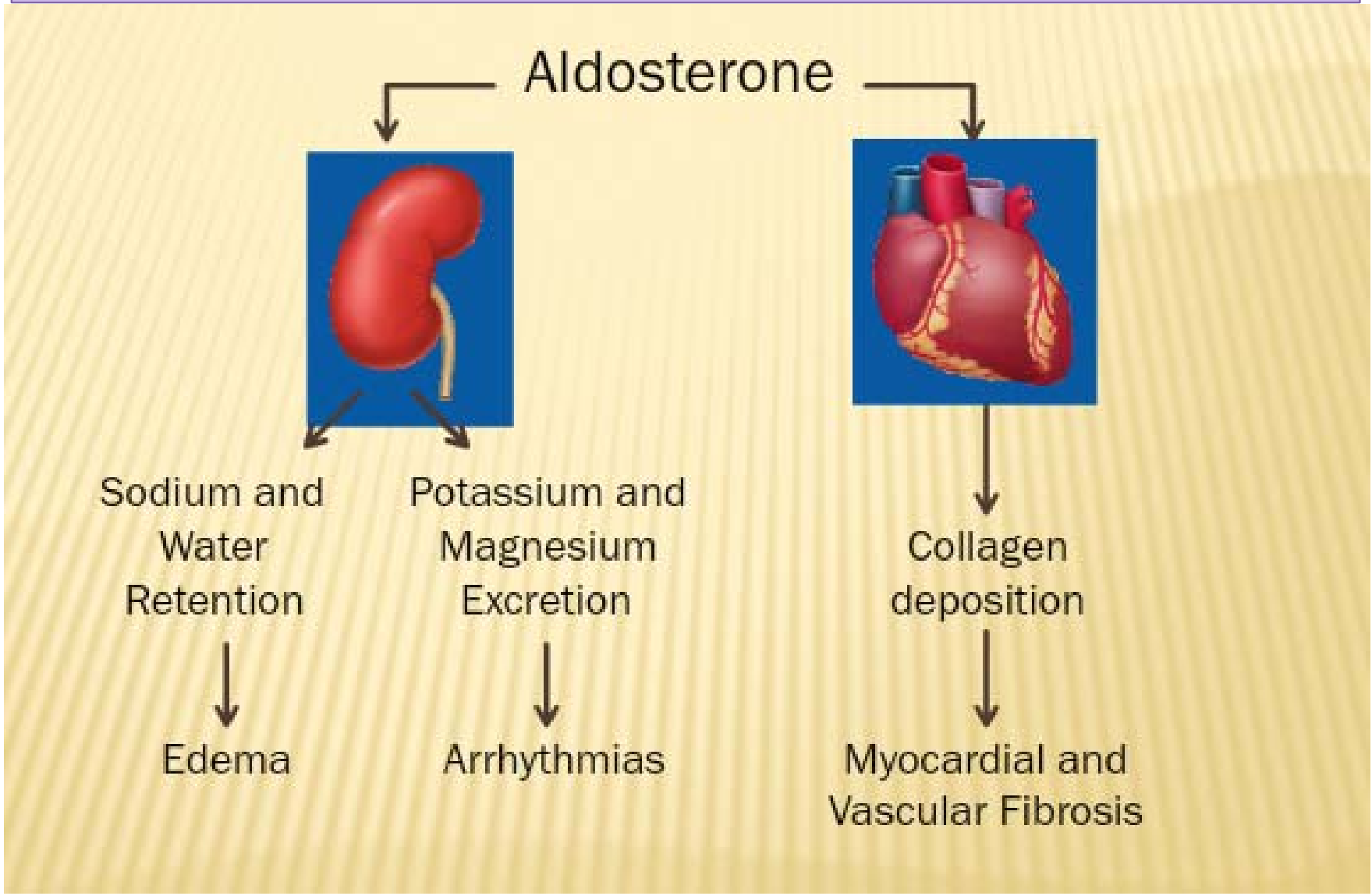
    1. Spironolactone
    2. Eplerenone

RAAS pathway



Kidney Int 2009: 76:23-31.

Action mechanism of aldosterone antagonist



Aldosterone antagonist

Characteristics	Spironolactone	Eplerenone
Clinical indication	Severe (NYHA class III–IV) CHF with LV systolic dysfunction	Severe (NYHA class III–IV) CHF after myocardial infarction
	Essential hypertension	Essential hypertension
	Primary hyperaldosteronism	
Receptor binding affinity (aldosterone = 1)	1.1×10^{-1}	5.1×10^{-3}
Sex-steroid receptor cross-reactivity	Yes	Minimal
Metabolism	Hepatic	Cytochrome P450, isoenzyme CYP3A4
Conversion to metabolites for effect	Yes	No
Half-life, h	1.4	4–6
Excretion	Renal and bile	Renal and GI
Administration	With food to maximize absorption	With or without food
Recommended dose, mg/d	Hypertension, 50–100; CHF, 25–200	Hypertension, 50–100; CHF, 25–50
Drug interactions	Potentiate hyperkalemia	Potentiate hyperkalemia
	ACE-I	ACE-I
	NSAIDs	NSAIDs
	Potentiate hypotension	CYP3A4 inhibitors increase eplerenone: itraconazole, ribonavir, clarithromycin
	Narcotics	CYP3A4 inducers decrease eplerenone: St John's wort
	Increase digoxin levels	
Side effects	Hyperkalemia	Hyperkalemia
	Gynecomastia, breast tenderness	Abdominal pain, diarrhea
	Erectile dysfunction	
	Dysmenorrhea, amenorrhea	

Spironolactone

- Nonselective aldosterone antagonist
- Metabolized in liver
- Plasma half life ~1.4h

  (if hepaatic congestion, duration increase x5)

- Max drug response 48h after 1st dose
- Structully similar to progesterone

  -> sex steroid receptor cross-reactivity

  -> antiprogesterone, antiandrogen effect

Eplerenone

- Selective aldosterone receptor antagonist
- Limited affinity for the progesterone and androgen reseptor

  -> lack sex-related side effect
- steady-state drug level 48h after 1st dose
- metabolized CytP450
- plasma half life 4-6h

Adverse effects

- Hyperkalemia (impairing aldosterone-mediated effects on K+ homeostasis in the primcipal cells in kidney)
- Hyperchloremic metabolic acidosis
- Gynecomastia
- Hirsuitism, impotence, menstural irregularitus

Aldosterone antagonist

Secondary Prevention

Aldosterone antagonist in UA/NSTEMI patients already receiving and ACE-I with LVSD (EF <0.40) and either symptomatic HF or DM

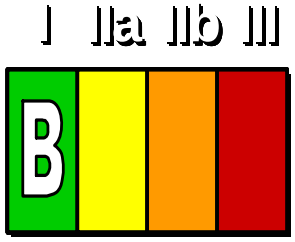
Aldosterone antagonist in those with LVSD (EF<0.35) and recent or current NYHA class IV HF symptoms*

ACE-I=Angiotensin converting enzyme inhibitor, DM=Diabetes mellitus, EF=Ejection fraction, HF=Heart failure, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, NYHA=New York Heart Association

*Contraindications include abnormal renal function (creatinine ≥2.5 mg/dL in men or ≥2.0 mg/dL in women) and hyperkalemia (K+ ≥5.0 meq/L)

Patients With Reduced Left Ventricular Ejection Fraction

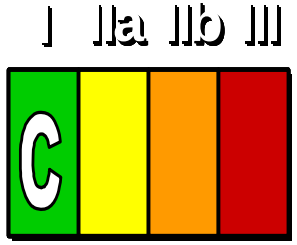
The Risks of Aldosterone Antagonists



Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine 2.5 mg/dL or less in men or 2.0 mg/dL or less in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.

The Hospitalized Patient

Intensifying the Diuretic Regimen



When diuresis is inadequate to relieve congestion, as evidence by clinical evaluation, the diuretic regimen should be intensified using either:

a. higher doses of loop diuretics;
b. addition of a second diuretic (such as metolazone, spironolactone or intravenous chlorthiazide) or
c. Continuous infusion of a loop diuretic.

ACCF/AHA PRACTICE GUIDELINE: PRACTICE GUIDELINE: FULL TEXT

2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults

Oral Diuretics Recommended for Use in the Treatment of Chronic Heart Failure

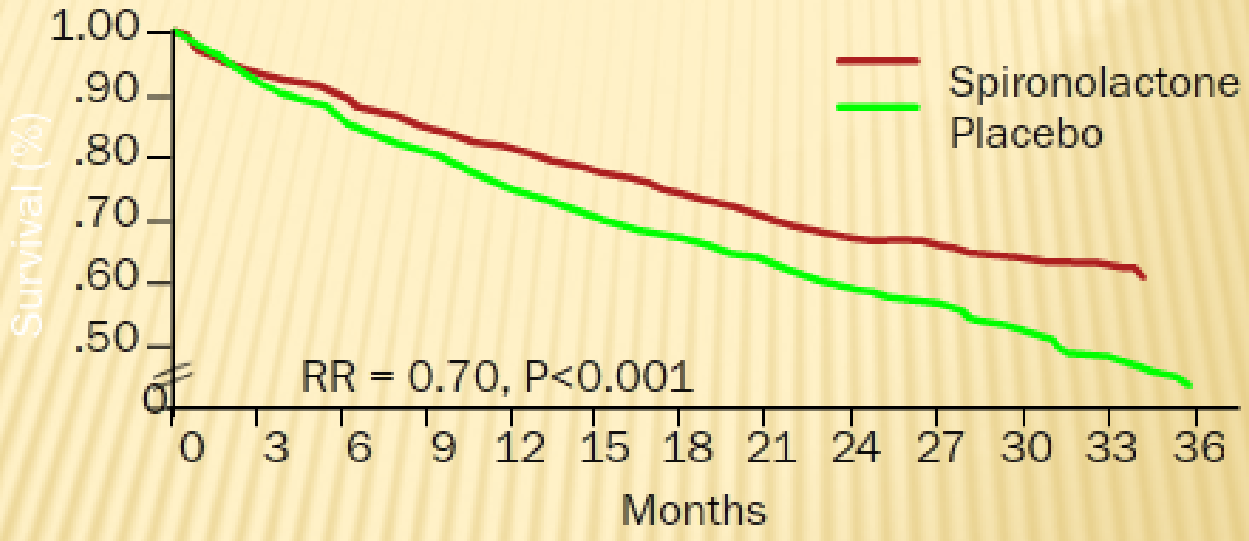
Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop Diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide Diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 mg once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-Sparing Diuretics*			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg†	2 to 3 days
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential Nephron Blockade			
Metolazone	2.5 to 10 mg once plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic		

* Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the rennin-angiotensin-aldosterone system.

† Higher doses may occasionally be used with close monitoring.

Randomized Aldosterone Evaluation Study (RALES)

1,663 patients with NYHA Class III or IV HF and LVSD (EF <0.35) randomized to spironolactone (25-50mg) or placebo for 24 months



Aldosterone inhibition reduces death in patients with advanced heart failure

Pitt B et. al. NEJM 1999;341:709-717

Spironolactone

- **Spironolactone,** should be considered for people with moderate to severe heart failure (NYHA grades III-IV) who are already on an ACE inhibitor and a loop diuretic [SIGN, 1999; DH, 2000; Samuel, 2003].
- **The Randomised Aldactone Evaluation Study (RALES)** compared treatment with low-dose spironolactone (25 mg daily) added to standard care with other diuretics, ACE inhibitors and digoxin against standard care alone, in people with moderate to severe heart failure (NYHA III-IV) [Pitt et al, 1999]. Mortality was reduced by 30%, the risk of hospitalization for worsening heart failure was reduced by 35%, and there was a significant improvement in symptoms. Over 2 years, one death was avoided for every 9 people treated with spironolactone in addition to standard therapy.
- **Careful monitoring for hyperkalaemia and hypovolaemia is required.** [Heart Failure Society of America, 1999; Krum, 2001; Remme et al, 2001]

HEART FAILURE

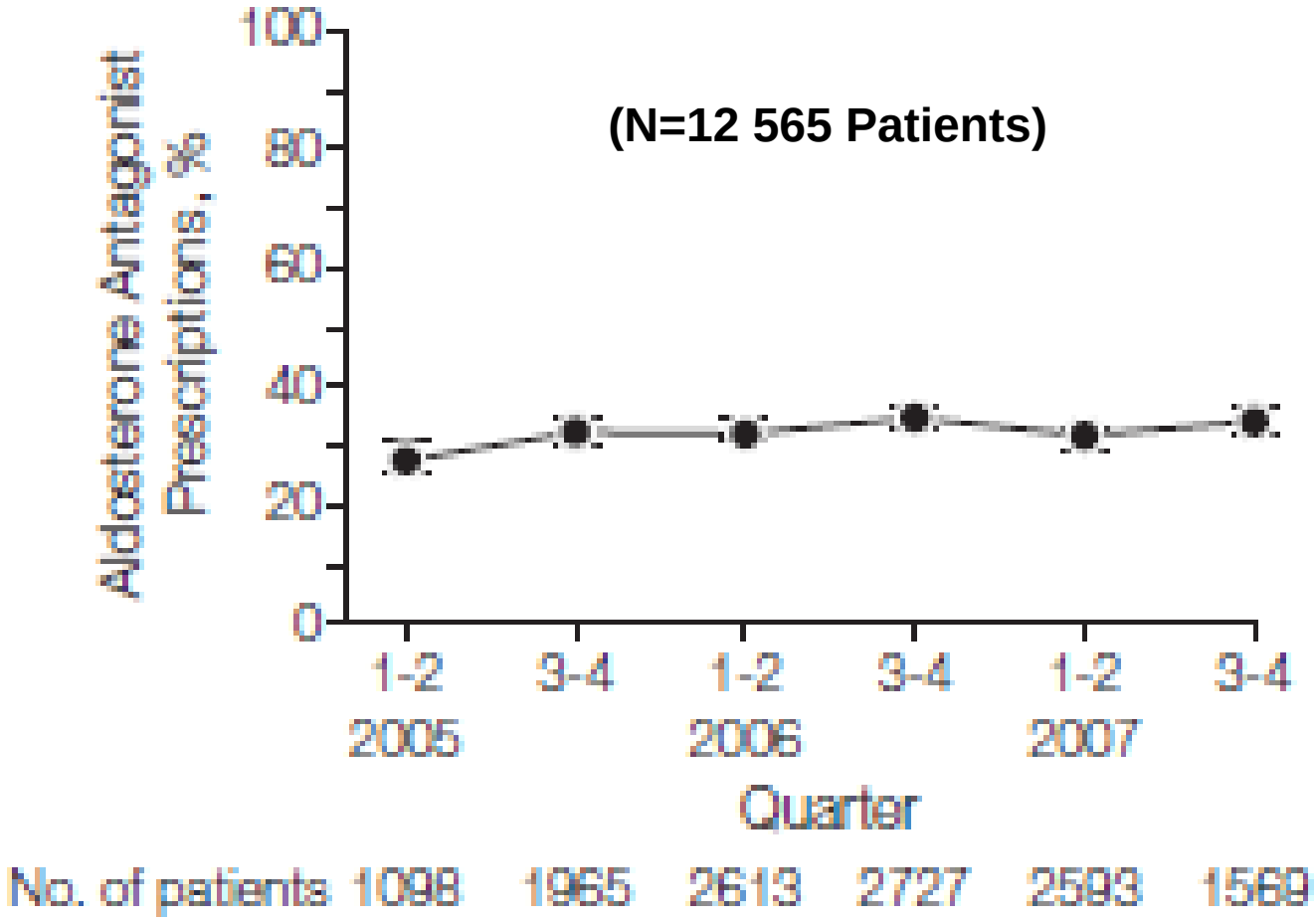
Aldosterone antagonists are underused by clinicians

Jane-Lise Samuel and Claude Delcayre

Aldosterone antagonists decrease the mortality of patients with heart failure, but an observational study by Albert and colleagues has found that a surprisingly low number of patients receive aldosterone antagonists before discharge from hospital. This article highlights potential reasons for why there is such an underuse of efficient drugs in heart failure.

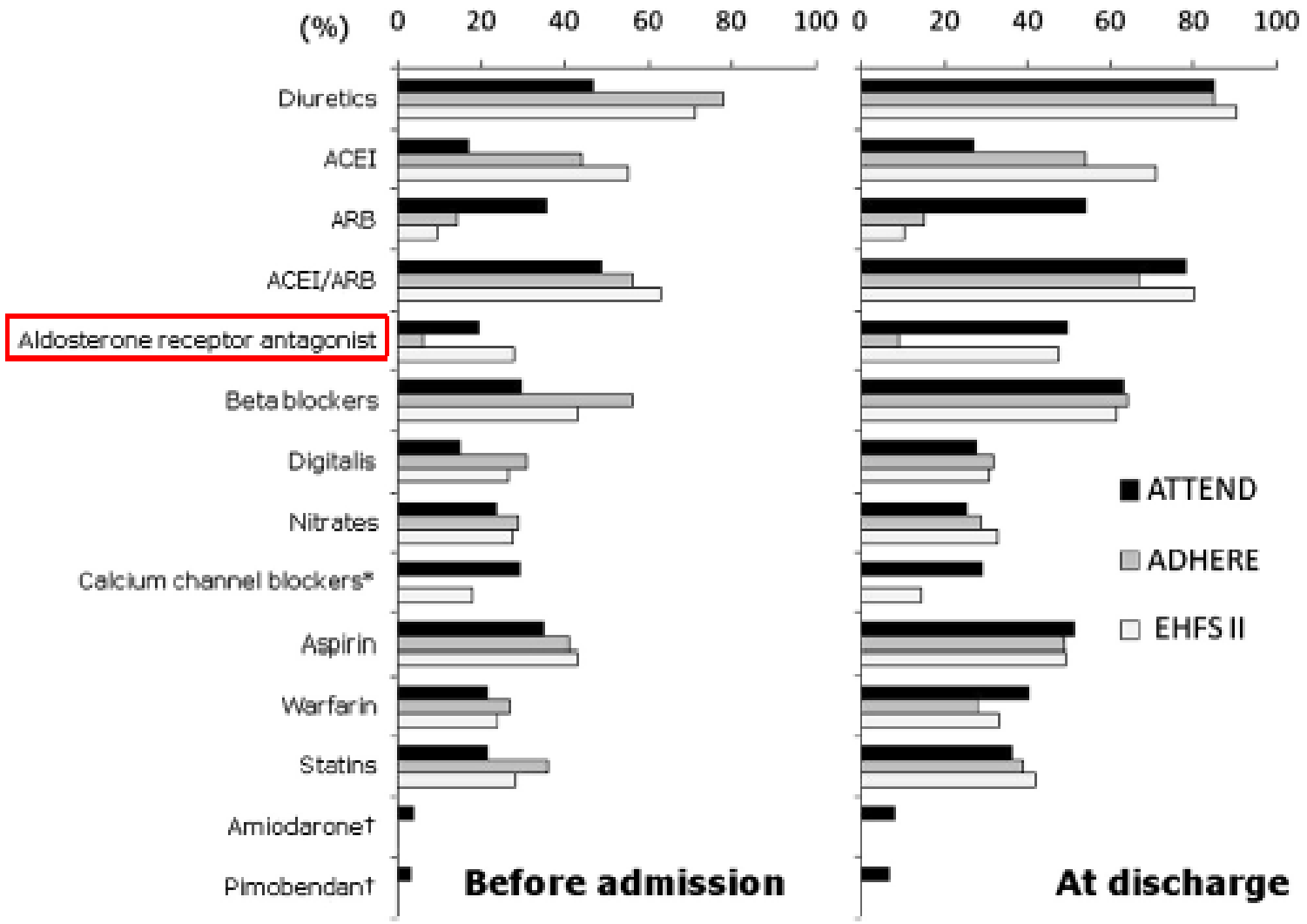
nature reviews cardiology 7 ; 2010:125

Aldosterone Antagonist Use



JAMA 2009;302(15):1658-65

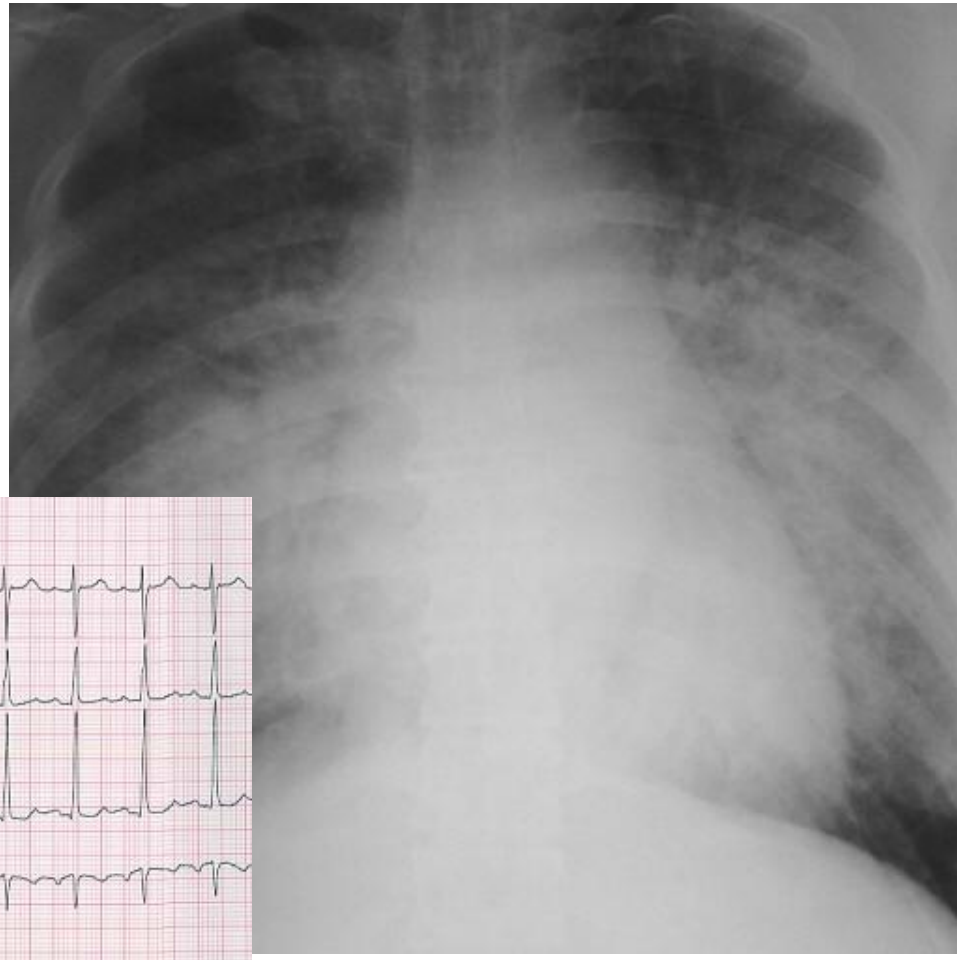
Prescribed rates of major oral medications before admission and at discharge in the present study

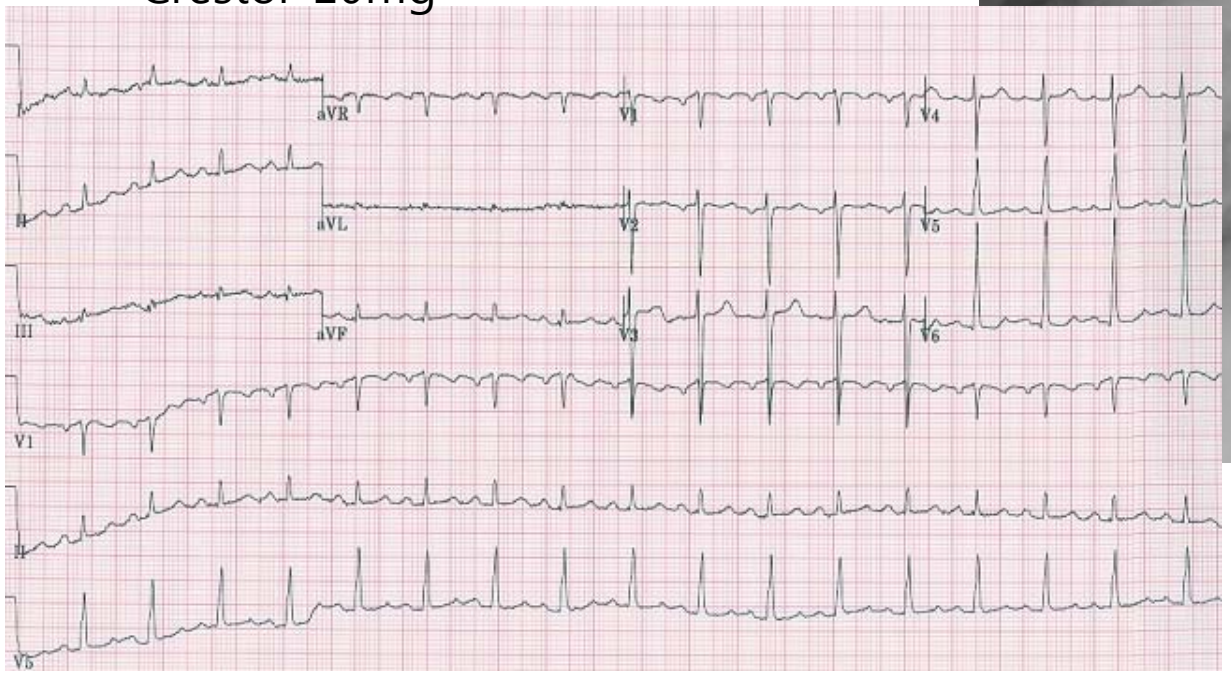


Am Heart J 2010;159:949

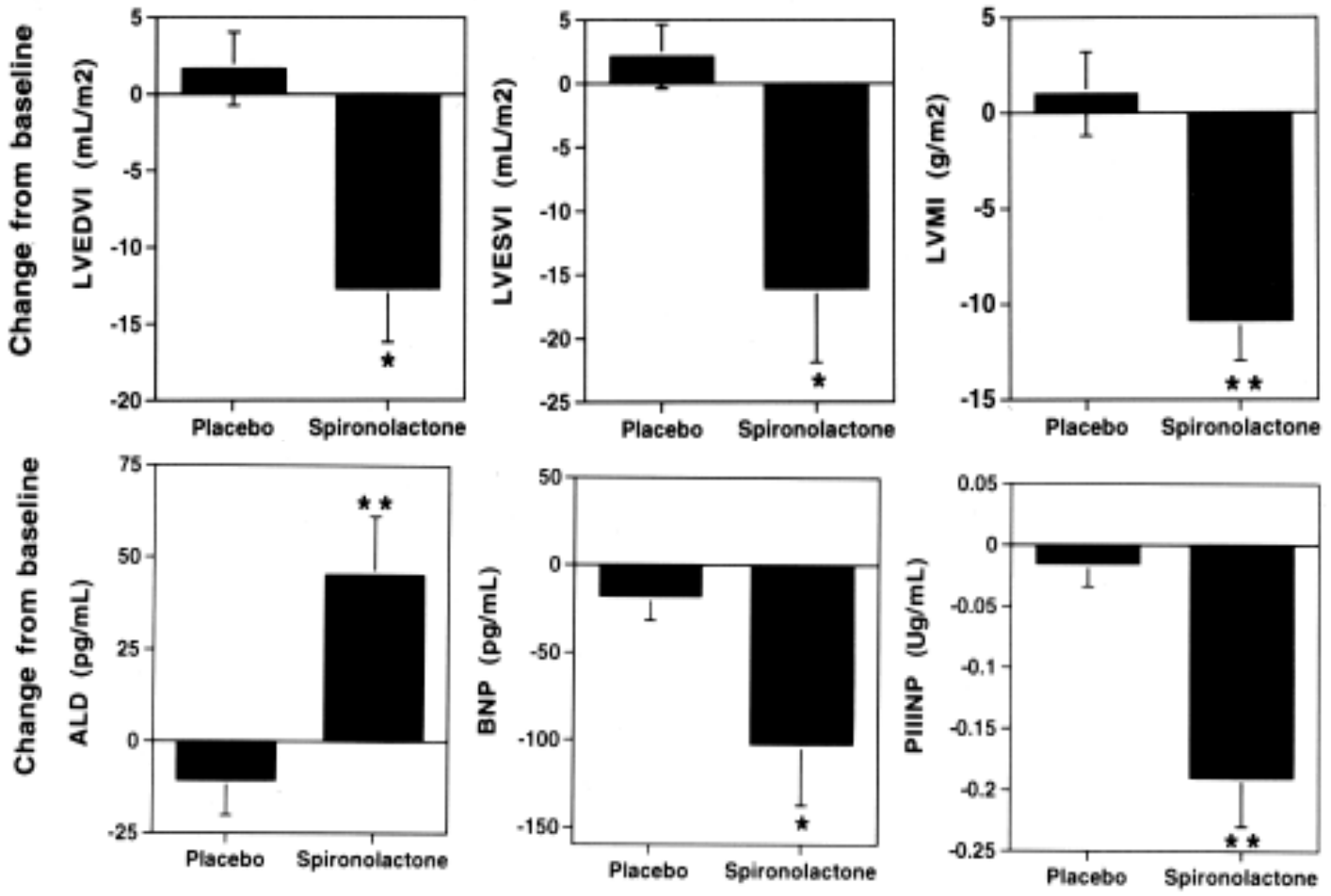
56/M Dyspnea

HTN (+), Ex-Smoker
Previous PCI due to MI 4years ago
EF 40%
Aspirin 100mg
Dilatrend 12.5mg
Diovan 80mg
Lasix 20mg
Crestor 10mg





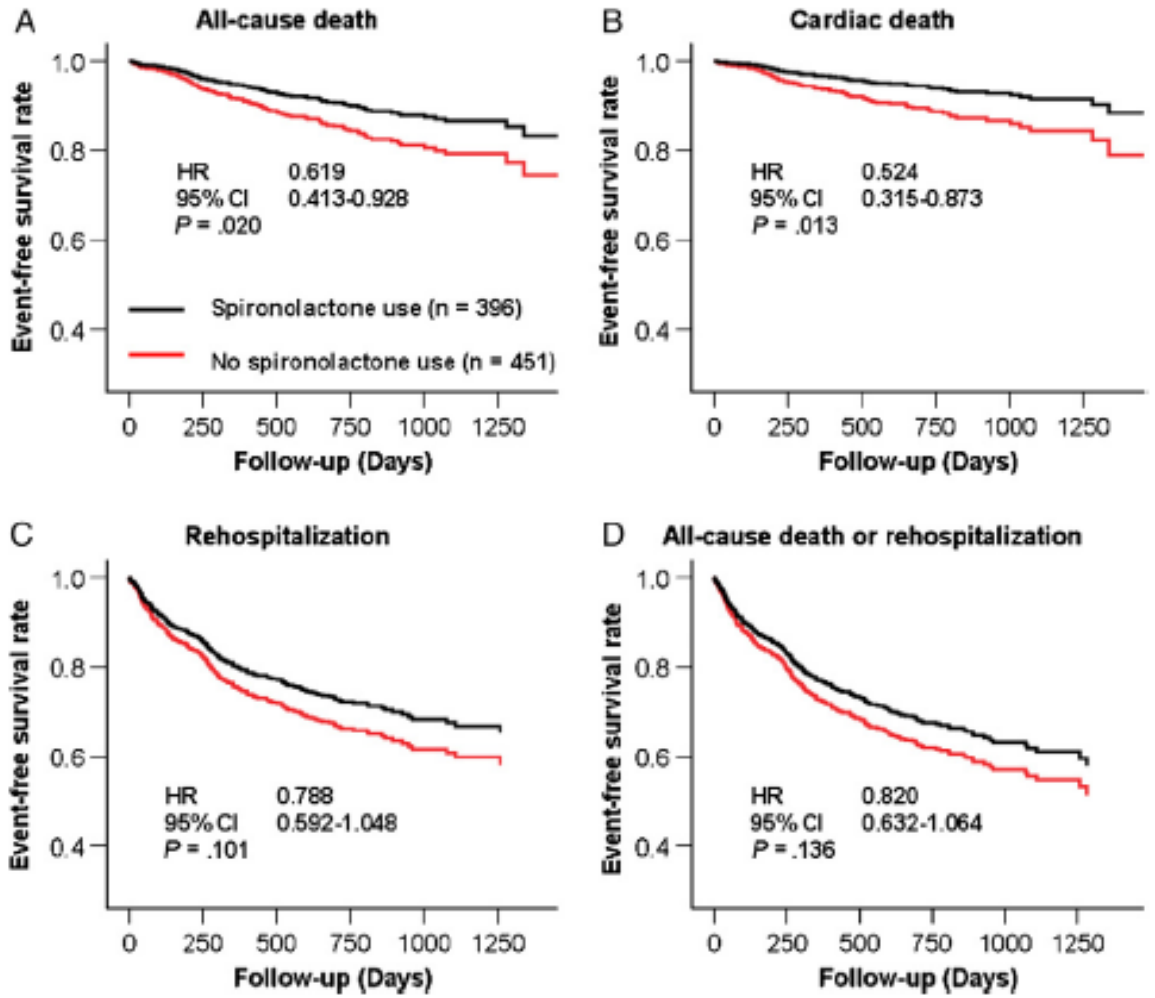
Effect of Spironolactone on Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling in Patients with CHF



J Am Coll Cardiol 2001;37:1228 –33

Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure

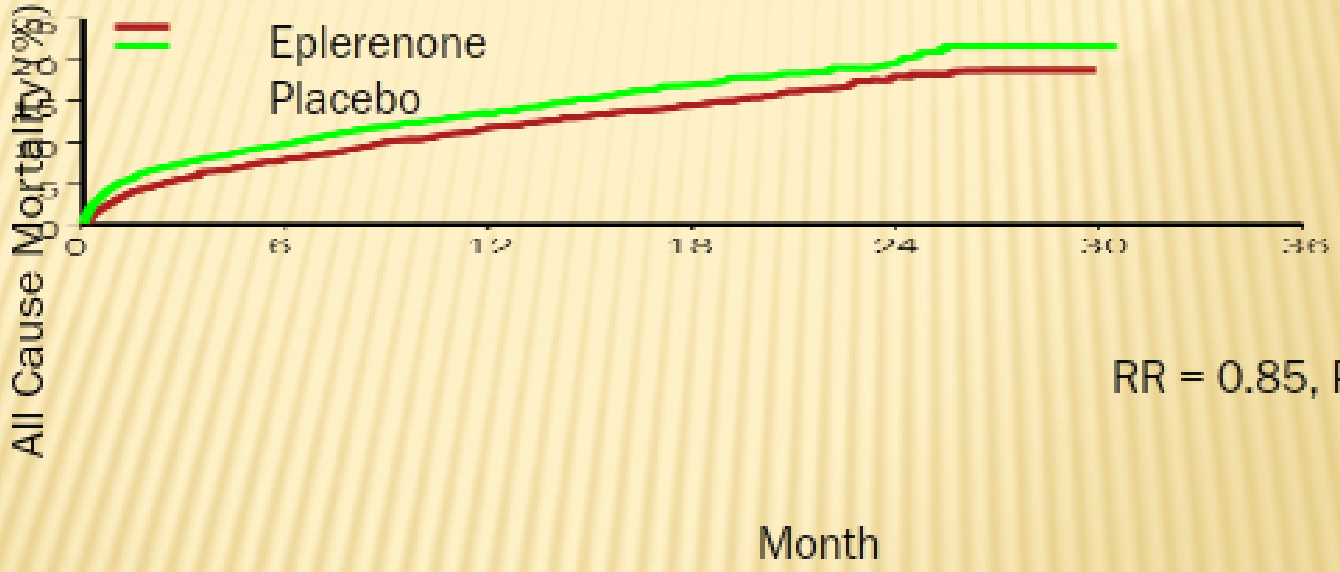
946 Pts
EF<40%



Am Heart J 2010;160:1156-62

Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS)

3,313 patients with evidence of HF and LVSD (EF <0.40) after a MI randomized to eplerenone (25-50 mg) or placebo for 16 months

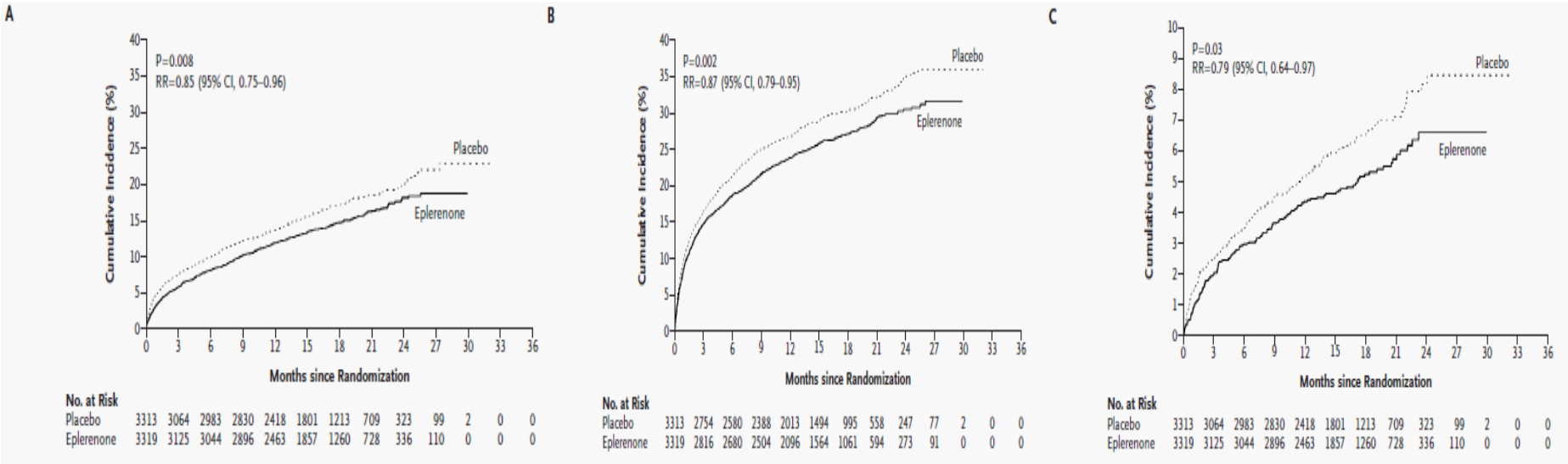


Aldosterone inhibition improves survival in patients with post-MI HF and LVSD

Pitt B et al. NEJM 2003;348-1309-21

Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

Bertram Pitt, M.D., Willem Remme, M.D., Faiez Zannad, M.D., James Neaton, Ph.D., Felipe Martinez, M.D., Barbara Roniker, M.D., Richard Bittman, Ph.D., Steve Hurley, B.S., Jay Kleiman, M.D., and Marjorie Gatlin, M.D., for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators*



Death from Any Cause

Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events

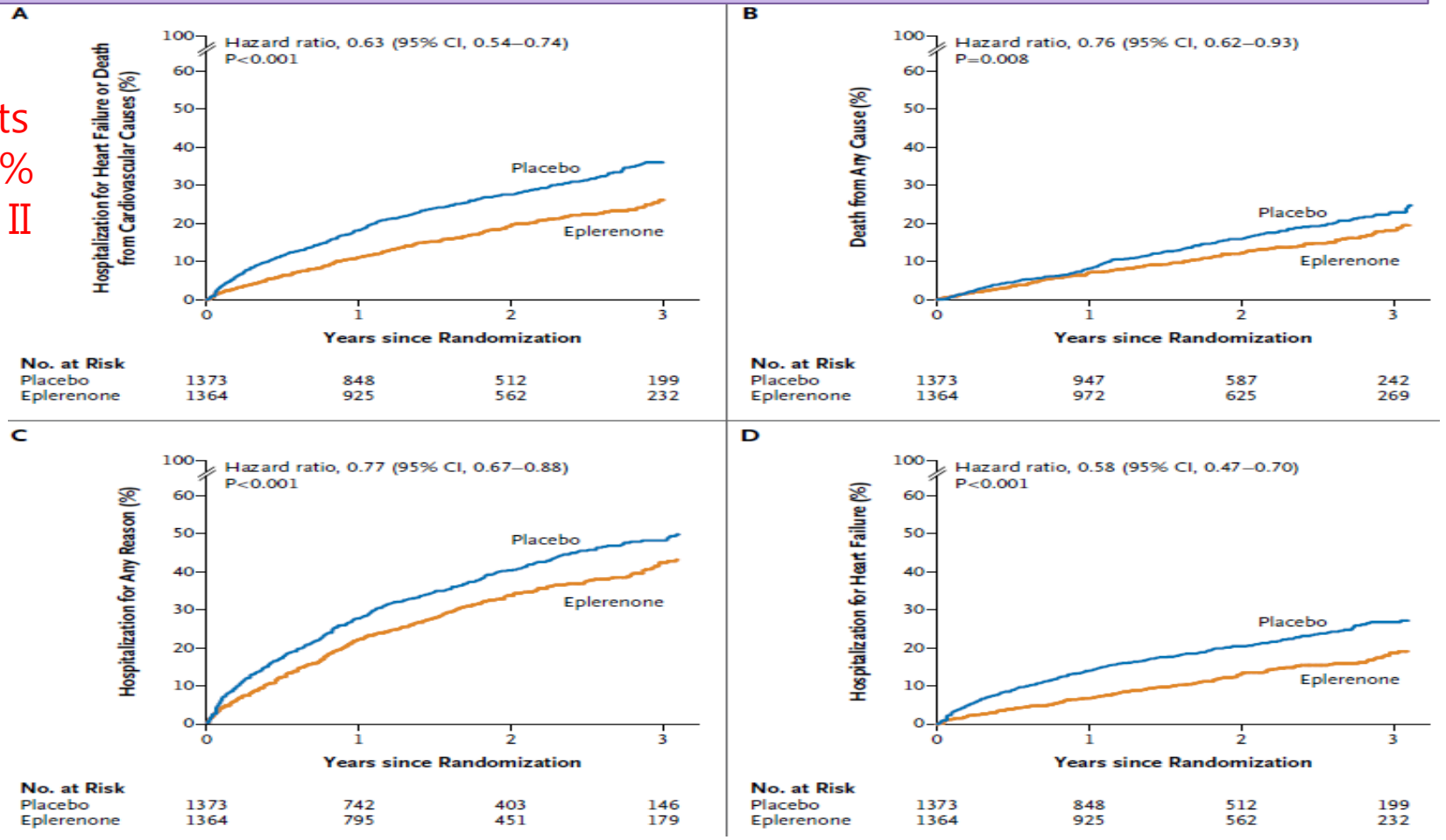
Sudden Death from Cardiac Causes

N Engl J Med 2003;348:;1309-21.

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

2737Pts
EF<35%
NYHA II



NEJM 2011;364:11

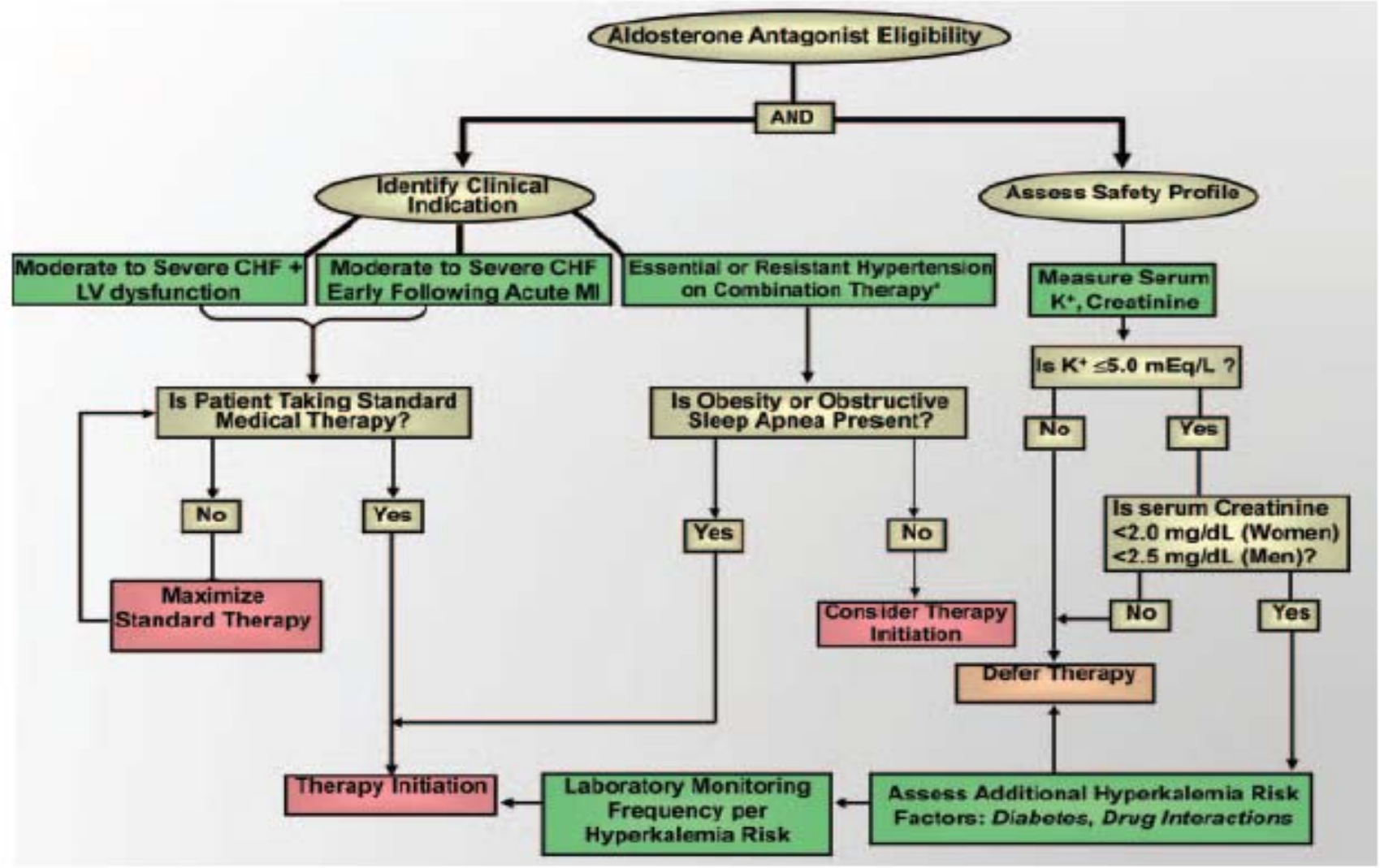
New biology of aldosterone

- Old concept:
  - Released from the adrenal cortex,
    ->circulated in the bloodstream,
  - Acted only on the kidney
  - Retain sodium and excrete potassium

- New concept:
  - Aldosterone is made in, including various organs: Vessels, Brain, Myocardium
  - many tissues also express mineralocorticoid receptors.
  - Aldosterone acts in a paracrine fashion in many organs.

Curr Opin Nephrol Hypertens 2008:17:44-50

Aldosterone receptor antagonist



Circulation. 2010;121:934-939

Chronic Heart Failure

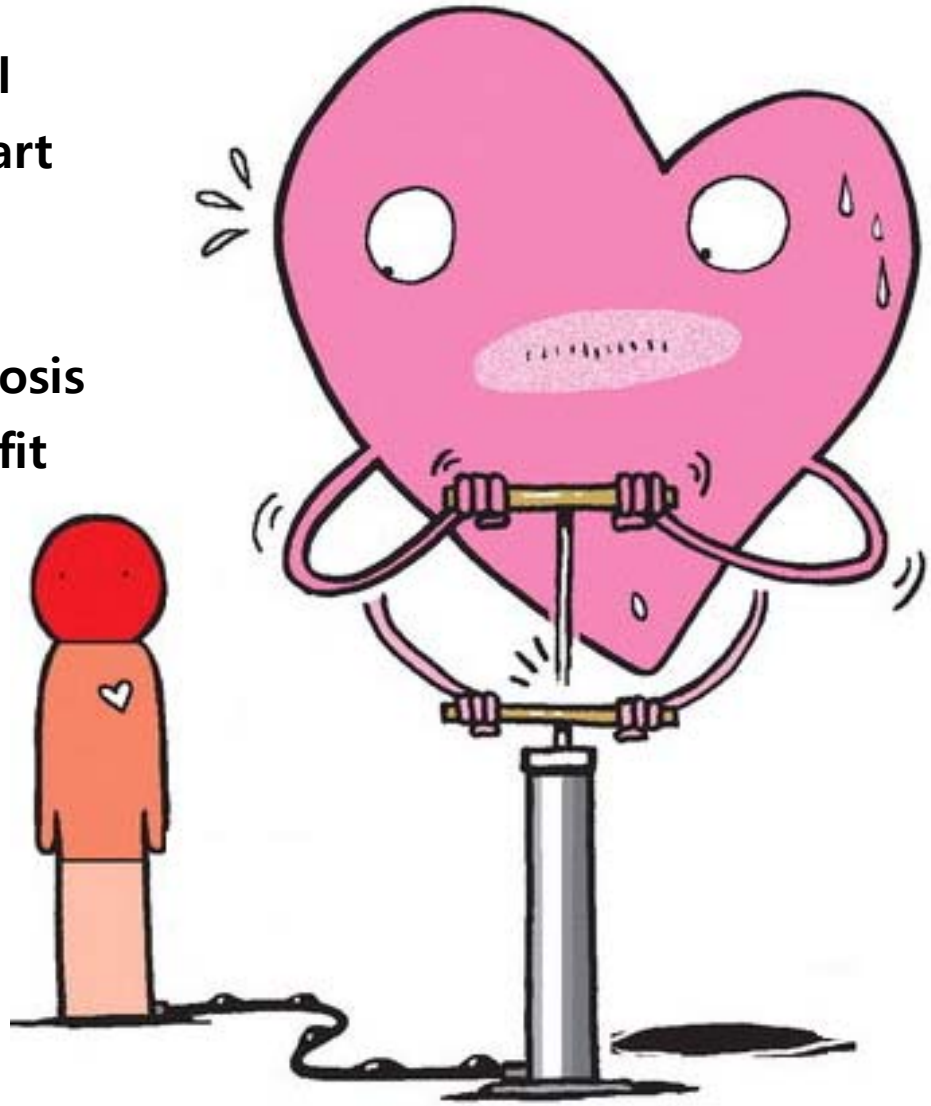
Symptom Control

Improving of Heart function

: EF, LV size

Improving prognosis

: Survival benefit



감사합니다.