Pharmacological treatment of congestive heart failure

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(CONGESTIVE) HEART FAILURE

- Syndrome of myocard inability to supply organs with blood characterized with **peripheral edemas, fluid retention and dyspnoe**

- **ASTHMA CARDIALE**

- FUNCTIONAL CLASSES **NEW YORK HEART ASSOCIATION (NYHA CRITERIA)**

Treatment goals of chronic HF

- Improve quality of life
- decrease frequency of dyspnoe episodes and decompensations
- Minimize patient`s invalidism

- **Delay the need for heart transplantation**

Target of pharmacotherapy

- Effects on **RAAS hyperreactivity**

- β-down regulation

  - Central
  - Myocardial
  - Renal

Basic pharmacotherapeutic groups used in treatment of heart failure

- **Monoamines and vasopressors**

- **β-blockers**
- **ACE inhibitors,**
- **AT-2 receptor blockers**
- **diuretics**
- **Inotropic agents**

Basic pharmacological groups in treatment of **acute heart failure**

- **Dobutamin i.v. (Dobutrex)**
  - Strong **β_1-agonist**
  - **High doses coupled with loss of selectivity**
  - Rapid onset of action(1-2 minutes), short blood halflife
  - **Potentiation of latent ventricular arrhytmias**
  - Therapeutic range 2,5 – 40 ug/kg/min !

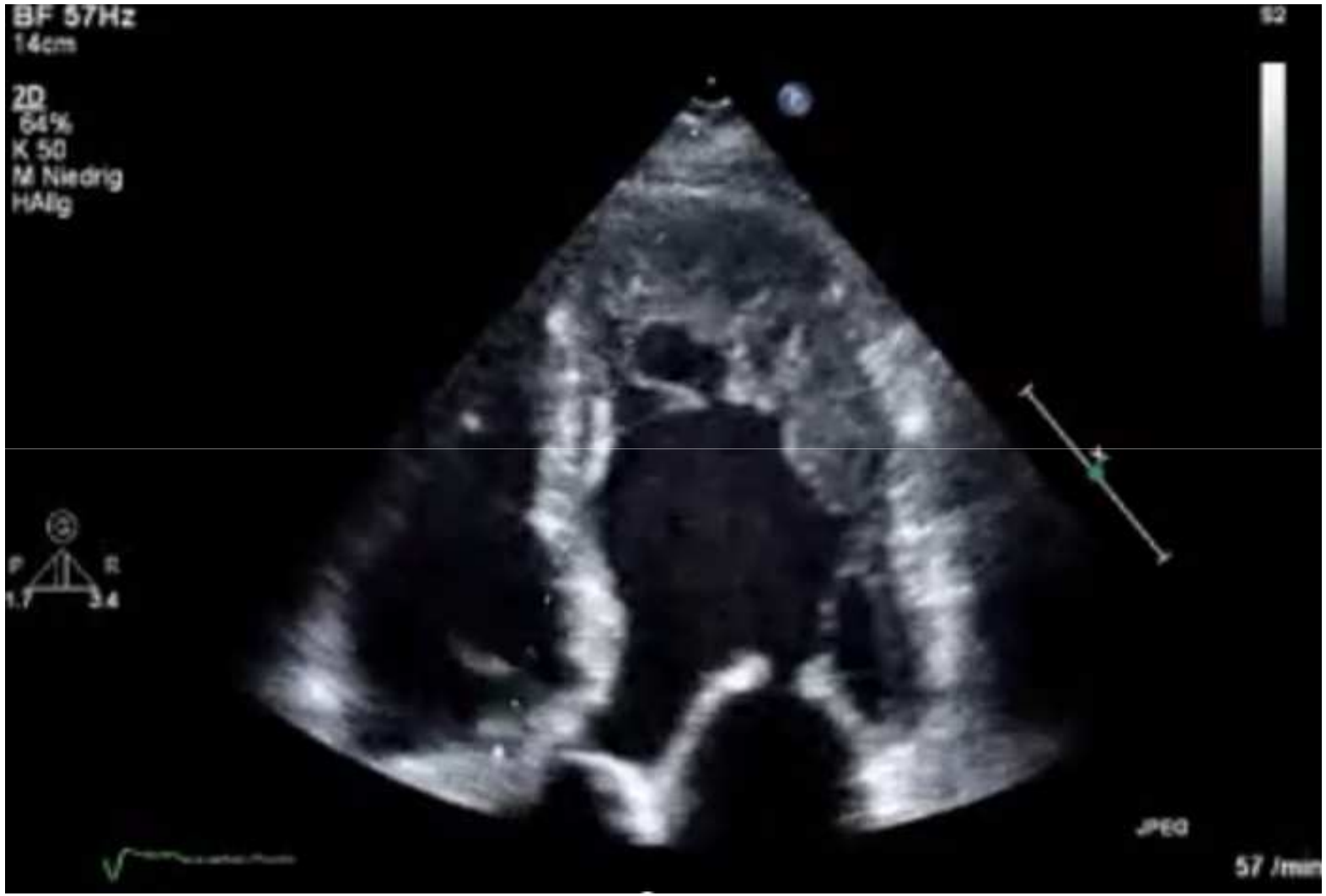
Basic pharmacological groups in treatment of **acute heart failure**

- **Noradrenalin i.v. (Noradrenalin Léčiva)**
  - α_1 a β_1 – combined agonist with **dose-dependent selectivity**
  - **≤ 2 ug/min** - β_1-selectivity + inotropy,

    + chronotropy
  - **4-10 ug/kg** - β_1-selectivity – increase **+CH, +I**
  - **≥ 10 ug/min** – increase peripheral vascular resistance

Factors affecting orally administered drugs

- Peripheral hypoperfusion
- **Cardiorenal syndrome**
- Compliance and confusion
  - encephalopathy in cerebral hypoperfusion
- Hepatic insufficiency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RAAS AND HF PROGRESS

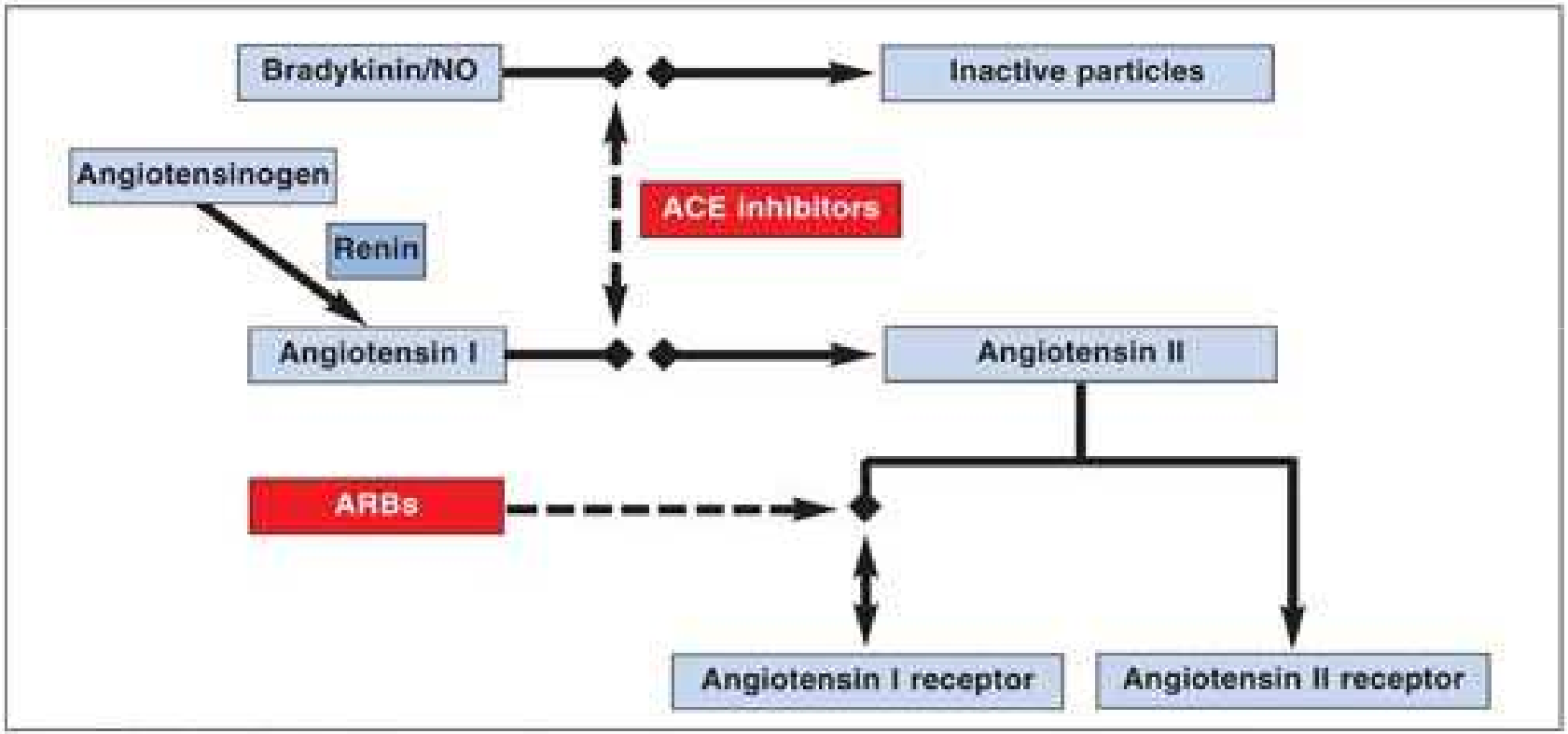


Figure 1. Renin-angiotensin-aldosterone pathway.
NO: nitric oxide; ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers.

Image reproduced: Dr. Macaulay T.:Cross-Reactivity of ACE Inhibitor–Induced Angioedema with ARBs

ANGIOTENSIN II

- Direct remodelation factor on LV
- Myocardium endotel smooth muscle cell proliferation
- Vasoconstriction and progression of renal insufficiency

iACE - advantages

- decrease of HF mortality
  - Kaptopril (**SAVE),** enalapril (**SOLVD**);
  - **Ramipril (AIRE), trandolapril (TRACE)**

- LV remodelation after myocardial infarction

iACE - advantages

- ↓ hospitalization count due to HF
- ↑ exercise tolerance and ↓ subjective difficulties

- **Always indicated in patients with symptomatic HF**
  - In absence of contraindication
  - ↓ risk of manifestation in patients without symptoms

Restrictions and adverse effects of iACE

- Renal failure
- History of angioneurotic edema
- Renal artery stenosis

- hypotension – titration „**start low, go slow**“
- Hyperkalemia with proteinuria
- Dry cough – change of therapy indicated ???

- **USE OF NSAID DECREASE THERAPEUTIC VALUE !**

Case of intolerance and contraindications – use of rAT-2 blockers

- Potential benefits resulting from rAT-2 block
  - remodelation
  - Hypertension treatment

- Vasodilatation due to increase availability of AT-2 to secondary receptors

- **Advantage – very good tolerance**
- **Disadvantage – lesser results in comparison to iACE (** ELITE II, ValHeFT a iné)

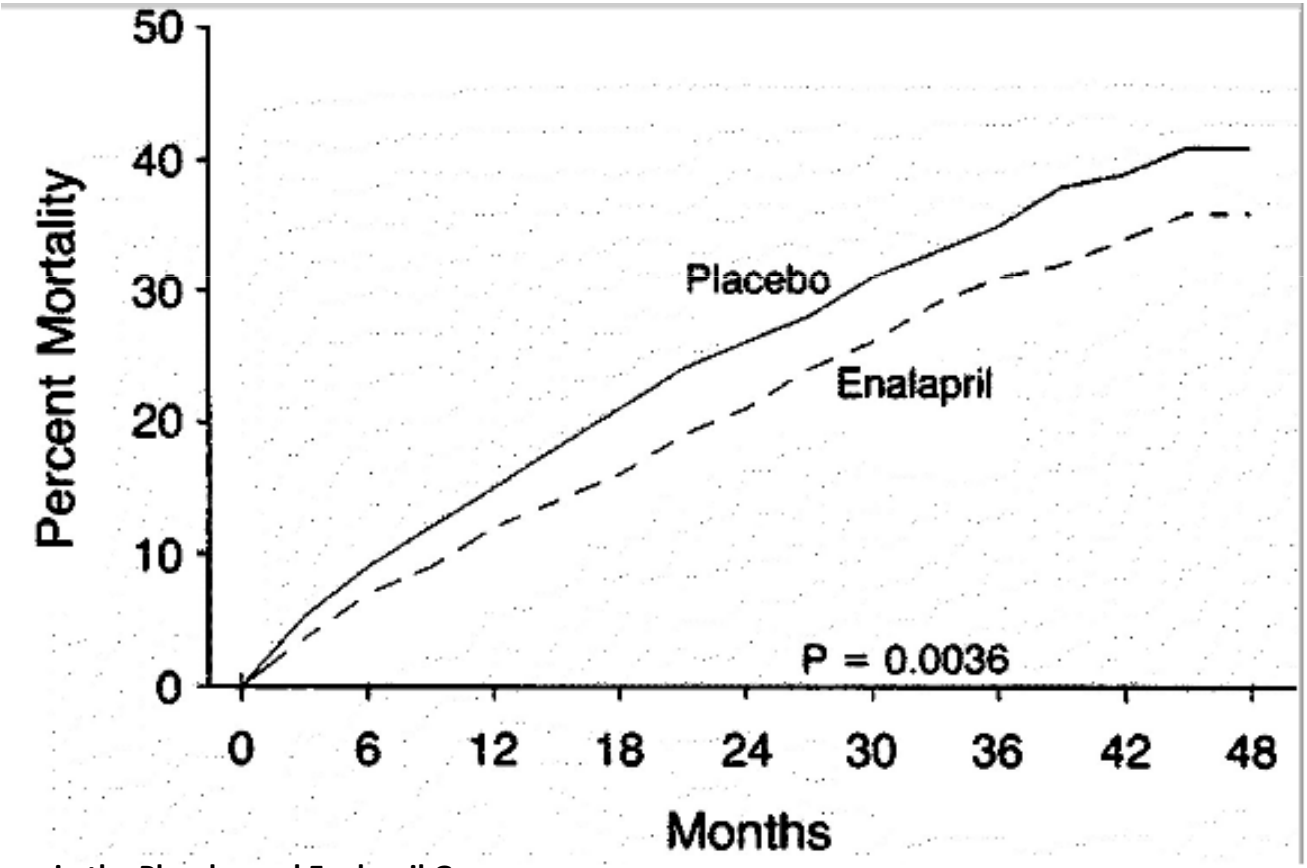
ACEi a HF (enalapril) – SOLVD-CURATIVE trial

- **Enalapril vs placebo** on standard therapy (BB+diuretics)
- Symptomatic patients with LV dysfunction

- Significant decrease of **mortality risk and hospitalisation count due to HF**

ACEi a HF (enalapril)

- **SOLVD-CURATIVE** studie



Mortality Curves in the Placebo and Enalapril Groups.

β-blockers and HF

- First attempt since 1975
- Negative inotropy concerns
  - HF represented long-time contraindication of BB
- Clinical trials
  - CIBIS I, II; MERIT-HF; COPERNICUS, CAPRICORN
- **Result - BB established as basic treatment of HF**

β-blockers and HF

- Average mortality decrease by 34%
  - **Risk of sudden death**

- **<u>Factors</u>**
  - Decrease of sympaticus **activation**
  - Decrease of **heart rate**
  - Diastola **prolongation**
  - Indirect β-receptor **up-regulation**

β-blockers - pleiotropy

- ↓ myocardium **oxygen consupmtion**
  - ACS, HF
  - Metabolism shift from *anaerobic* glycolysis to oxidative phosphorylation

- **β-receptor sensitisation**
  - Protective effect against high catecholamine plasma concentration
  - ↓ RAAS activation

β-blockers and HF - restrictions

- bradycardia
- Hypotension

- Asthma bronchiale
- Metabolic adverse effects
- Induction of coronary arthery spasms

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)

- Bisoprolol evaluation vs placebo in symptomatic patients
- NYHA III-IV

- Study design
  - ACEi + diuretika + BISOPROLOL
  - ACEi + diuretika + placebo
- **Untimely terminated due to ethical reasons !**

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial ; CIBIS-II Investigators and Committees
The Lancet - 2 January 1999 (Vol. 353, Issue 9146, Pages 9-13) , DOI: 10.1016/S0140-6736(98)11181-9

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF)

- Evaluation of metoprolol (12,5 mg/25 mg) vs placebo in HF (standard therapy)

- Pacients with HF NYHA II-IV
- Slow titration up to 200 mg
- *Follow-up* 1 year

- **Untimely terminated due to ethical reasons !**

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF)
MERIT-HF Study Group *The Lancet* - 12 June 1999 (Vol. 353, Issue 9169, Pages 2001-2007) DOI: 10.1016/S0140-6736(99)04440-2

The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure

- Evaluation of **carvedilol** vs placebo in patients with HF based on standard therapy
  - Digoxin + ACEi + diruetics
  - EF LV < 35 %
  - Significant mortality reduction
- **Untimely terminated due to ethical reasons !**

Packer M. et al.: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Eng J Med*. 1996; 334: 1349-1355

Clinical implications

- Expansion of pharmacotherapy of HF
- ACEi + diuretics + **β-blockers**
- **Cardioselective β-blockers without ISA**
- Increase LV EF and reverse remodelation

- **β-blockers on same level of therapeutic value in HF as iACE !**

Diuretics and HF

- Decrease of water retention
  - Antiedematous and hypotensive activity
  - Decrease of filling pressure in myocardium
  - Decrease of pulmonary congestion

Diuretics and HF

- **loop diuretics – furosemid,** torasemide**,**
- **sulfonamides – HCHTZ, chlorthalidon, indapamid**
- Aldosterone antagonists
  - spironolactone
  - Eplerenone
  - (finenrenone) – clinical trials

Diuretics and HF – adverse effects

- Mineral imbalance
  - Hypokalaemia (digitalis glycosides)
  - Hyperkalemia (spironolakton)
  - hypomagnesemia

- Metabolic adverse effects

Diuretics and HF

- **FUROSEMIDE**
  - Dose dependent diuresis
  - Without estimated maximum dose

  - **Long time administration** of loop diuretics leads to nephron hypertrophy and failure of excretion mechanisms in nephron loop

    - **diuretic resistance**

Diuretics and HF

- Monitoring K^+ and minerals (Na^+, Cl^-, Ca^{2+})

- Acute heart failure in i.v. formulation **continual infusion** or i.v. bolus
  - Bowel edema

DIURETIC RESISTANCE

- Inability of kidneys to excrete 90 mmol Na^+
- After administration of oral dose of furosemide

- 2x 160 mg in period of 72 hrs

  [Epstein et. al., 1977]

DIURETIC RESISTANCE

- Causes ???

  - Absorption failure due to bowel edema, possible bowel mucose blood hypoperfusion
  - Renal hypoperfusion

  - Long-time administration of high dose diuretic therapy (**loop hypertrophy**)

DIURETIC RESISTANCE

- **SOLUTION ?**
  - Low dose of sulfonamide diuretics
  - Hydrochlorothiazide 12,5 mg – 25 mg in combination with loop diuretics

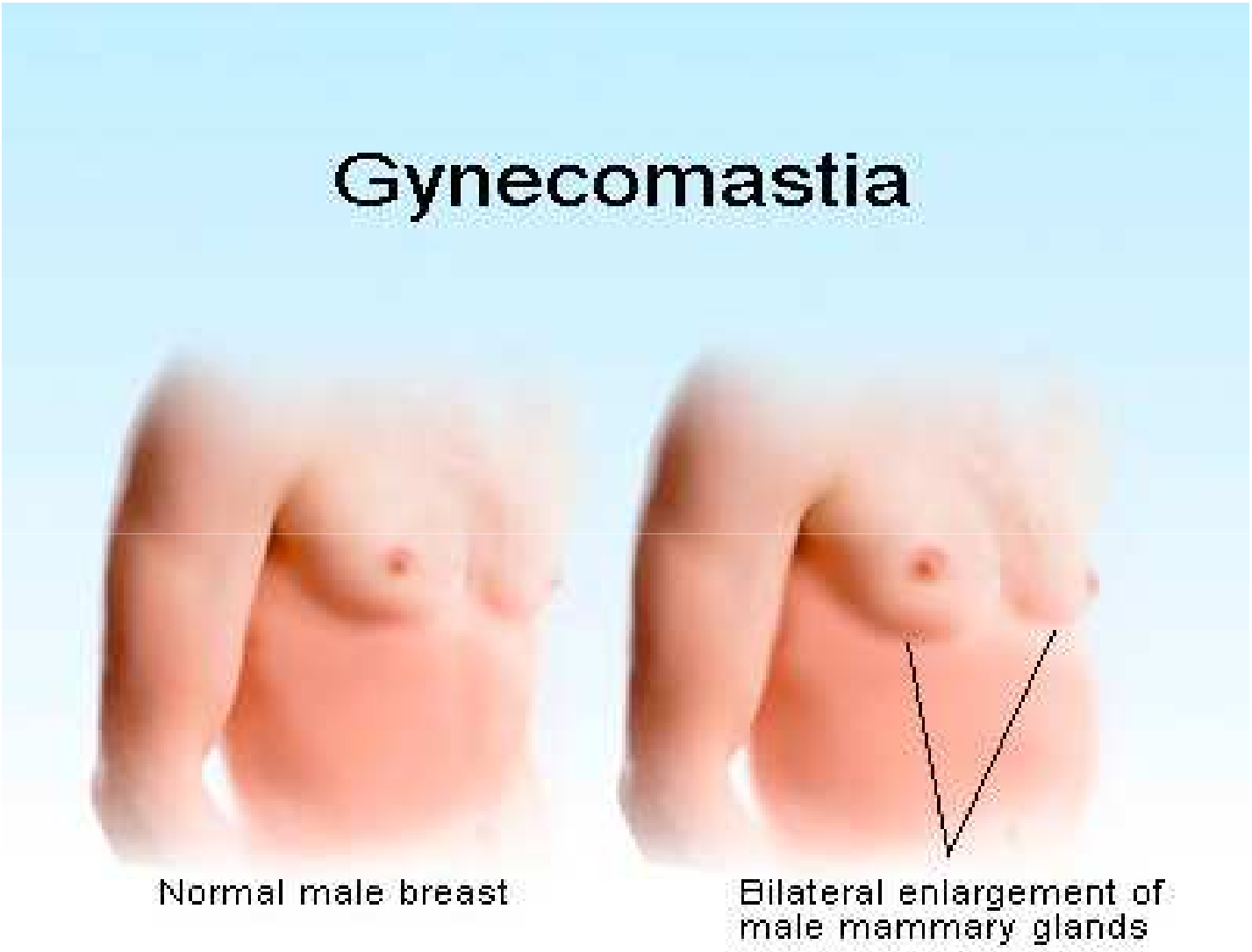
Spironolactone

- Aldosterone antagonist
- Absent diuretic activity
- Prevents loss of potassium and protone
  - Sodium and cloride secretion in distal tubulus

- **Inhibition of LV remodelation**

- 10 % male patients - gynecomastia

Gynecomastia

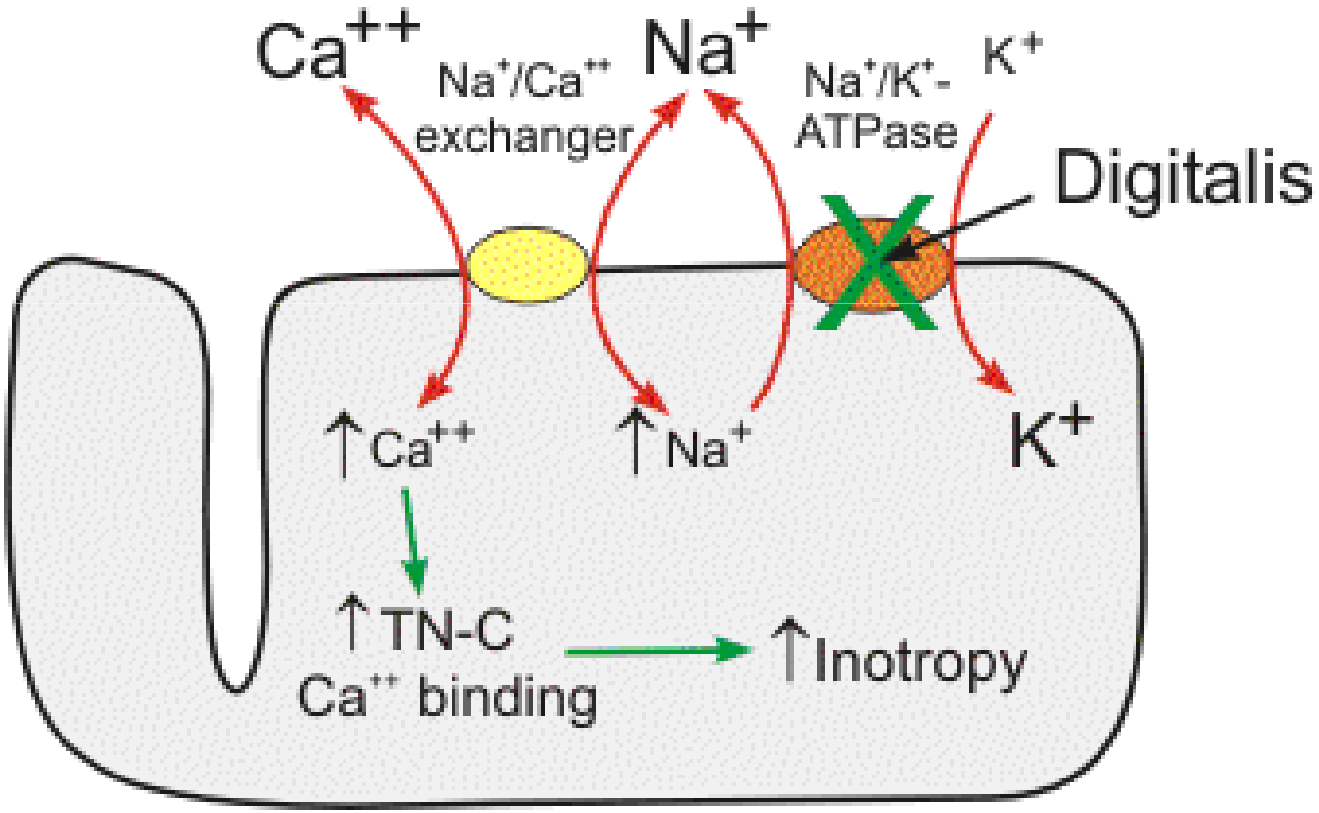


EPLERENON (INSPRA, PFIZER)

- Selective aldosterone antagonist
- Advantageous properties of spironolactone

- Without hypertrophy effects of spironolactone

Digoxin and HF – mechanism of effect and toxicity



Digoxin and HF

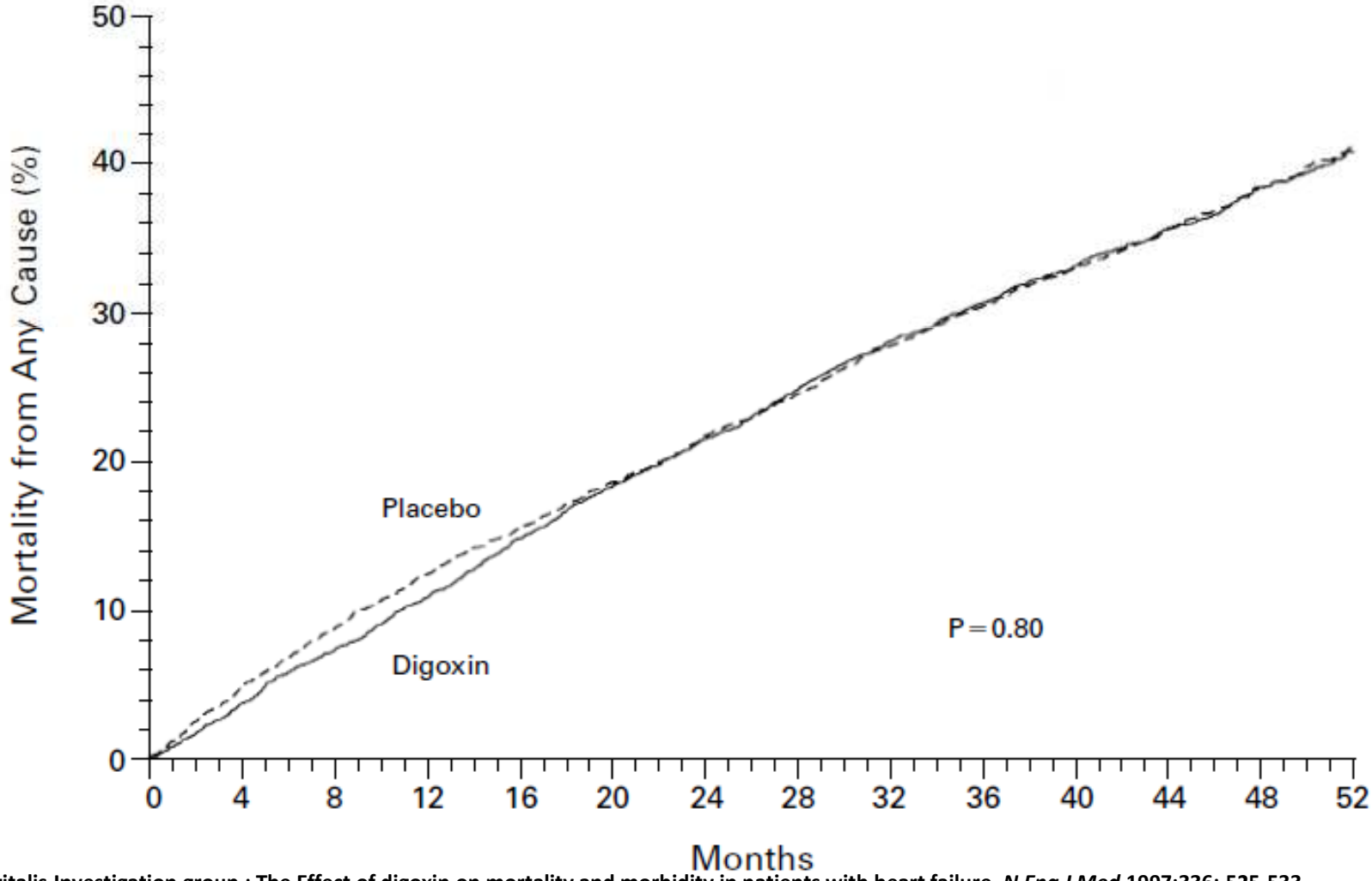
- Block Na^+/K^+-ATPase
- **DIG trial**
- 0,125 – 0,250 mg p.o.
- 0,500 mg i.v. -
- Requires TDM (**0,5-1,5 ng/mL**)

- Risk of toxicity increases in corelation to diuretic dose and patient age

Digoxin and HF

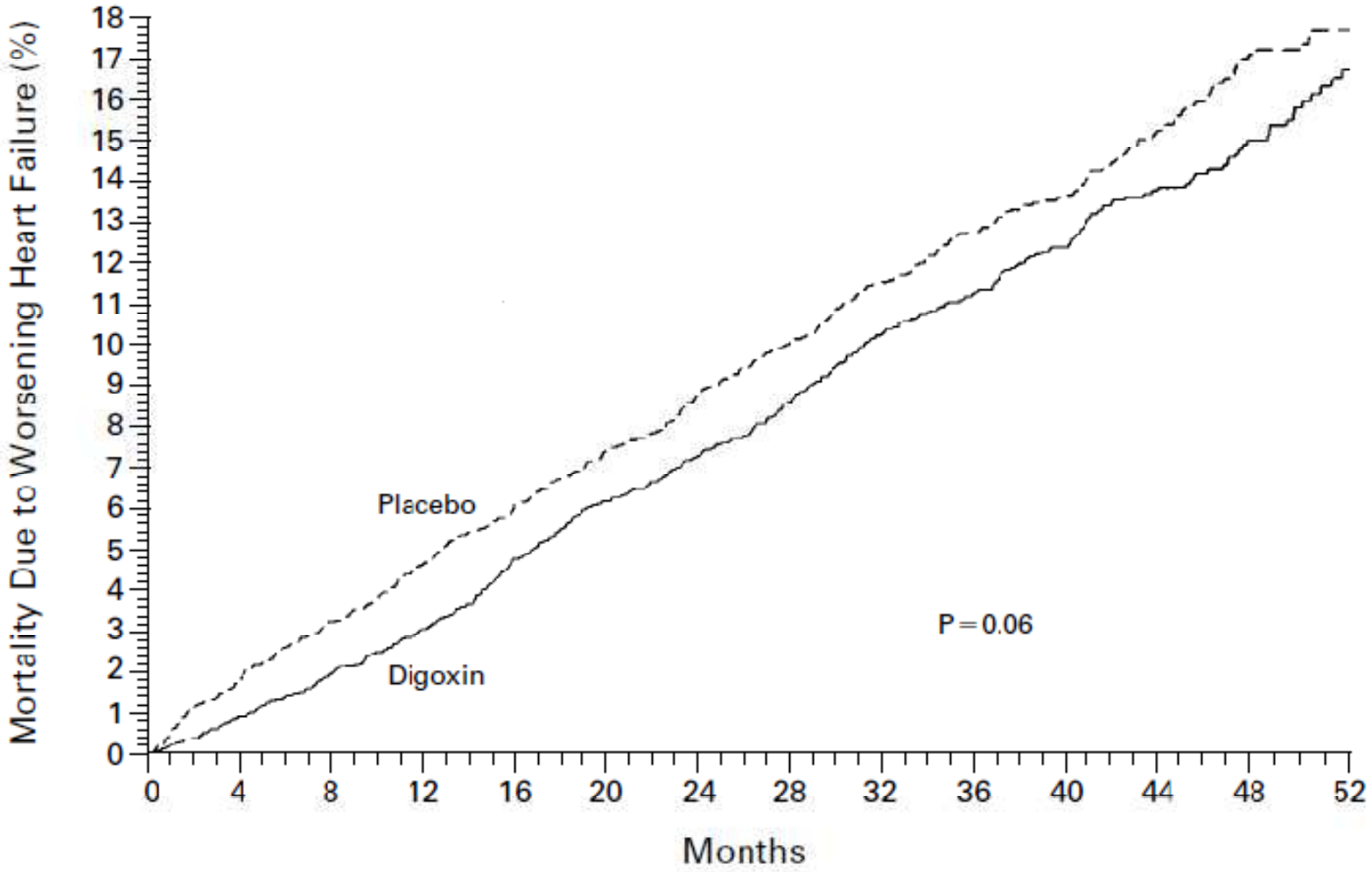
- Binding to albumin (25 %) and tissue distribution (skeletal muscles)
- p-glycoprotein substrate
- Enterohepatal circulation

Digoxin – CVS mortality data



The Digitalis Investigation group.: The Effect of digoxin on mortality and morbidity in patients with heart failure. *N Eng J Med.*1997;336: 525-533

Digoxin – HF mortality data



The Digitalis Investigation group.: The Effect of digoxin on mortality and morbidity in patients with heart failure. *N Eng J Med.*1997;336: 525-533

Novel molecules in developement for HF treatment – clinical trials in progress

- OMECAMTIV MECARBIL

- SERELAXINE
- ULARITIDE

OMECAMTIV MECARBIL

- Myosine activator
  - Cardiotonic activity

- 2.phase of clinical trials finished
  - HF decompensation

- Good p.o. bioavailability

OMECAMTIV MECARBIL (AMGEN)

- 2nd phase clinical trial
  - Tested parenteral administration

- 75 mg/L i.v. infusion
  - 4 hrs loading dose
  - 44 hrs maintenance dose
- Dose dependent limiting factor
  - Myocardium ischemia

Thank you

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