Treatment strategy of acute and chronic heart failure

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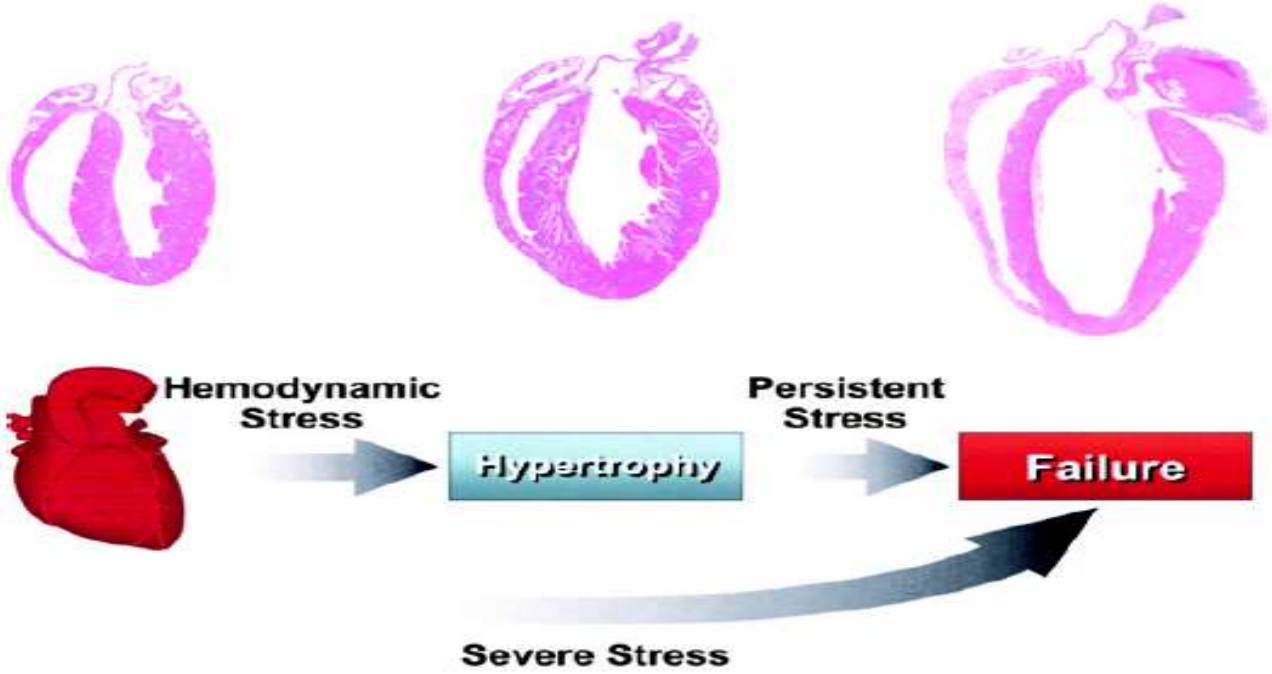
DEFINITION OF HEART FAILURE

Heart failure is a clinical syndrome (not a single disease) 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 and ESC HF guidelines

American Heart Association

EUROPEAN SOCIETY OF CARDIOLOGY®



HEART FAILURE

Definition: decrease of cardiac output (unable to provide sufficient tissue perfusion of the peripheral organs)

Key step of the therapy – identification of the etiology:

- Ischemic heart disease
- Toxic damage (cytostatic drugs, heavy metals, drug abuse, irradiation)
- Chronic arterial hypertension, peripartum hypertension
- Arrhythmia (tachy- or bradyarrhythmias; e.g. atrial fibrillation)
- Valvular insuficiency, cardiomyopathys (genetic, infection)

Types:

- systolic or diastolic heart failure

  reduced contractility – EF < 40% reduced (**HFrEF**)

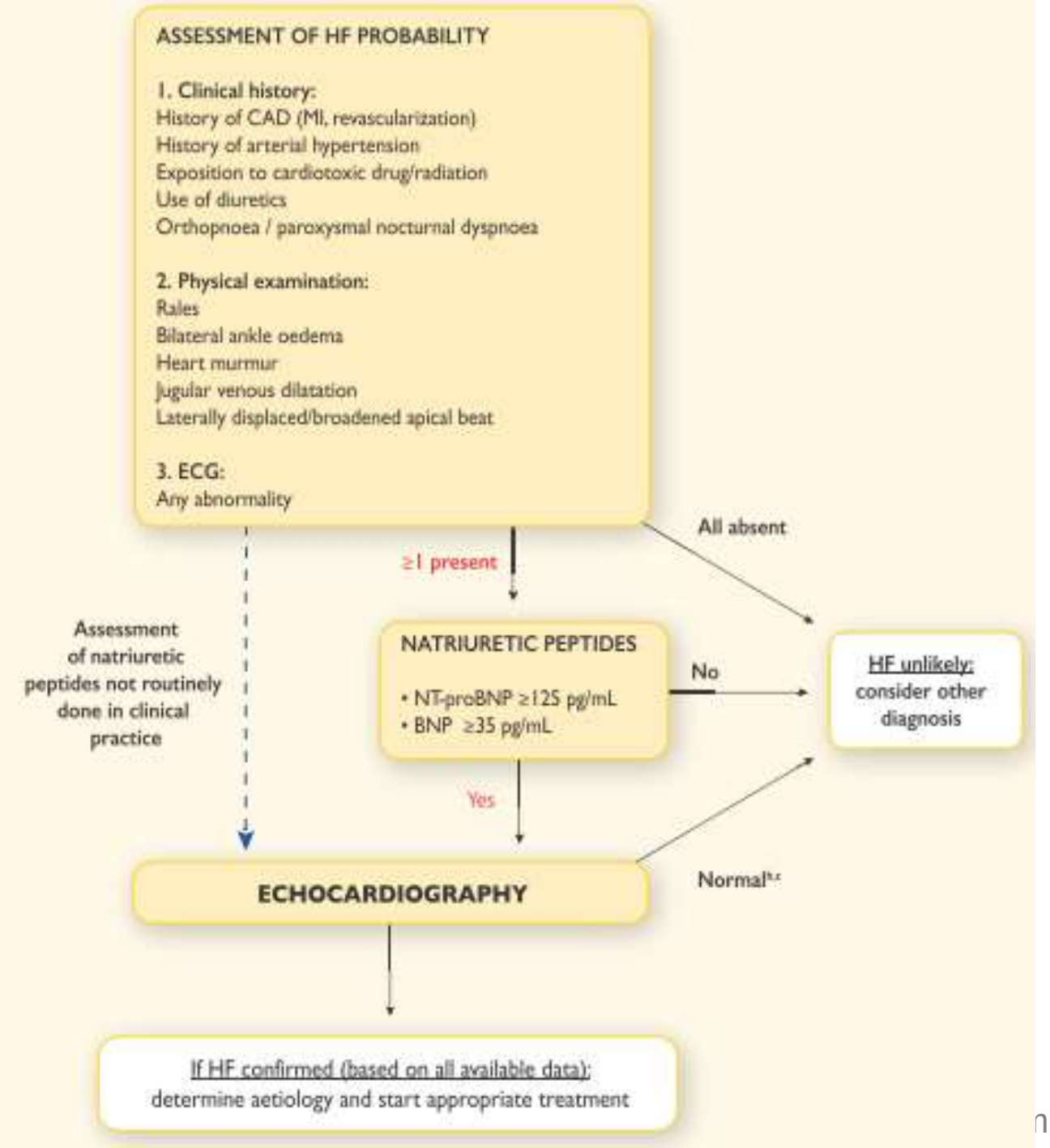
  reduced relaxation – EF 40-49% mild range (**HFmEF**)

  – EF> 50 % close to normal (**HFpEF**)
- acute or chronic

Symptoms & diagnosis:

- 4 stages (NYHA, ACC/AHA), fatigue, edema, EF, serum biomarkers e.g. BNP, etc

Diagnosis of non-acute HF

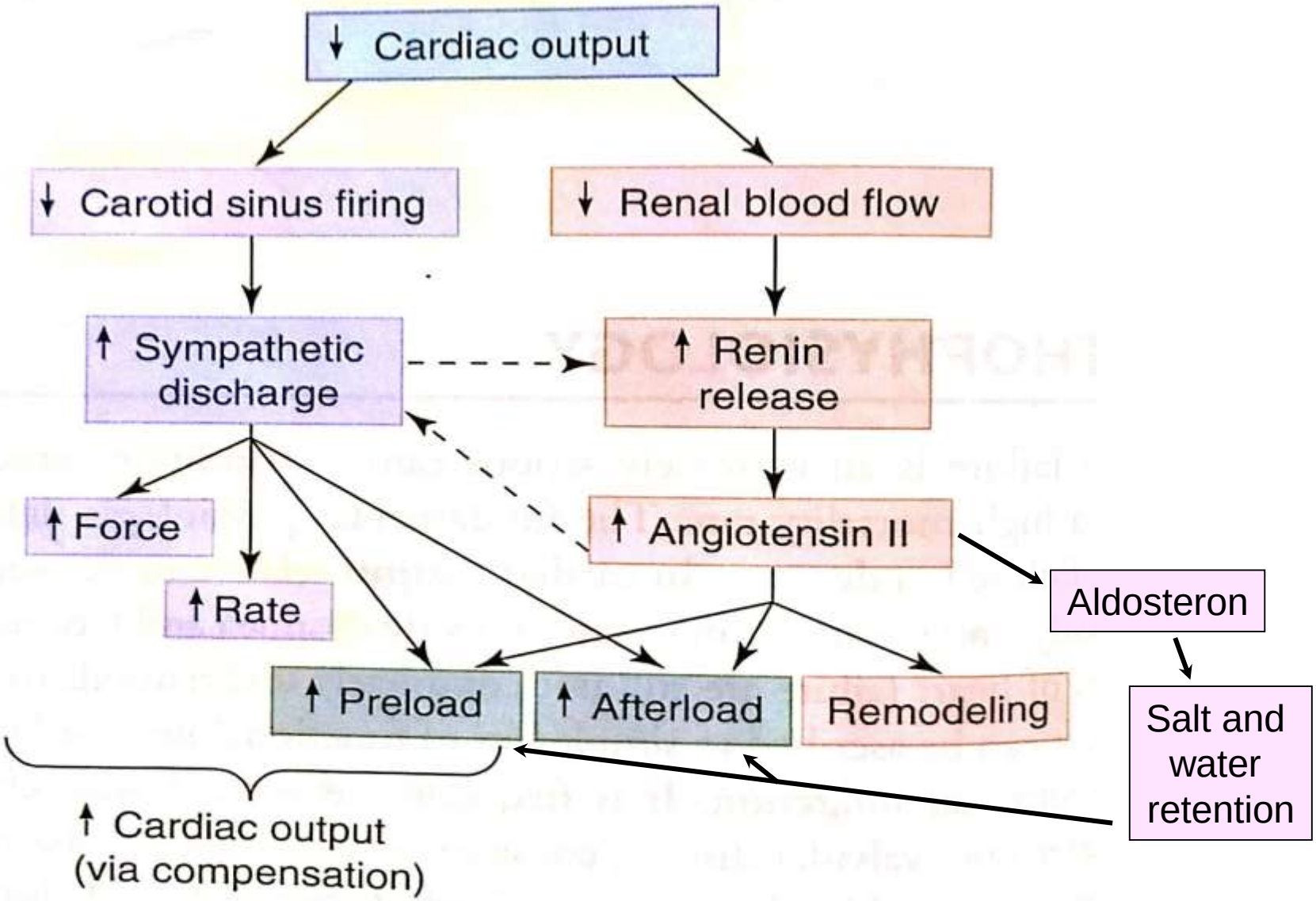


NYHA STAGES OF HEART FAILURE

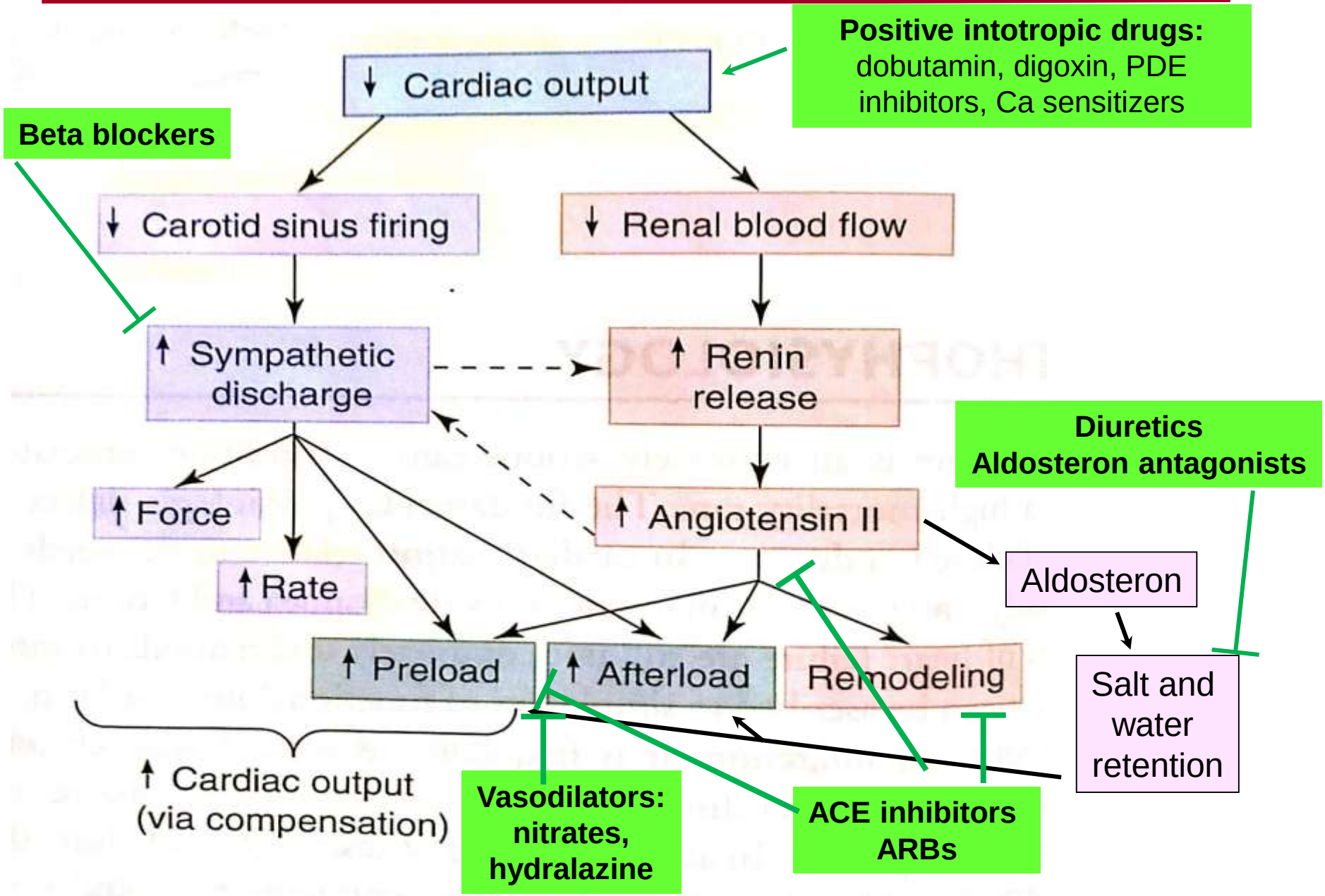
Stages of severity of cardiac state and dyspnoe according to the New York Heart Association (NYHA)

Grade of severity	Cardiac function	Dyspnoe	Mortality
Stage I	Not restricted	None	< 5%
Stage II	Slightly restricted	Dyspnoe at strong exercise	10%
Stage III	Moderately restricted	Dyspnoe at slight effort	20 - 30%
Stage IV	Severely restricted	Dyspnoe at rest	30 - 80%

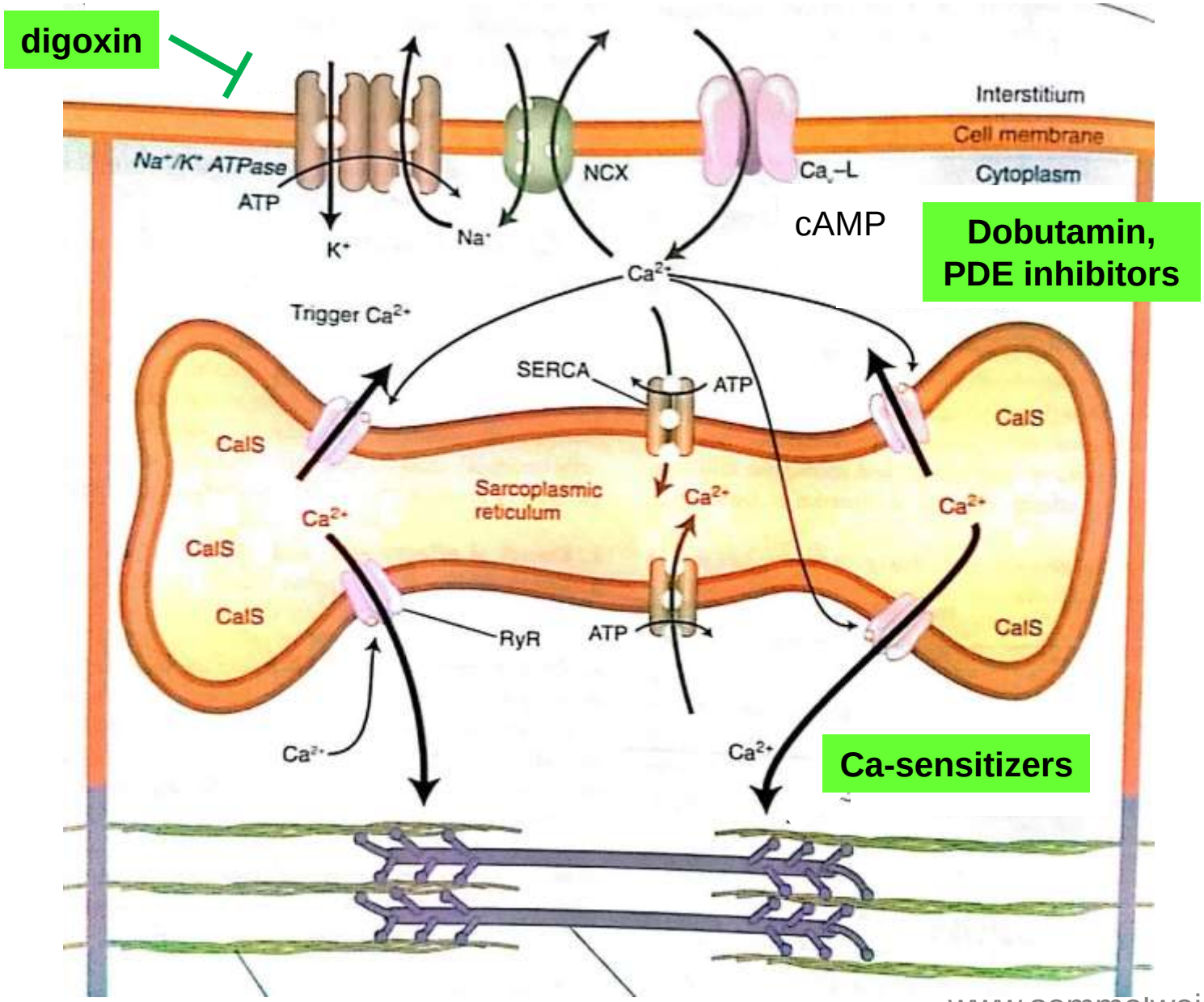
HEART FAILURE PATHOPHYSIOLOGY



Drug treatment of HEART FAILURE



HEART FAILURE CELLULAR MECHANISMS



TREATMENT OF HEART FAILURE

Aim:

- reduce high mortality
- improve quality of life by prevention of symptoms
- reduce irreversible remodelling and myocardial damage

1. Prevention and non-pharmacological treatment:

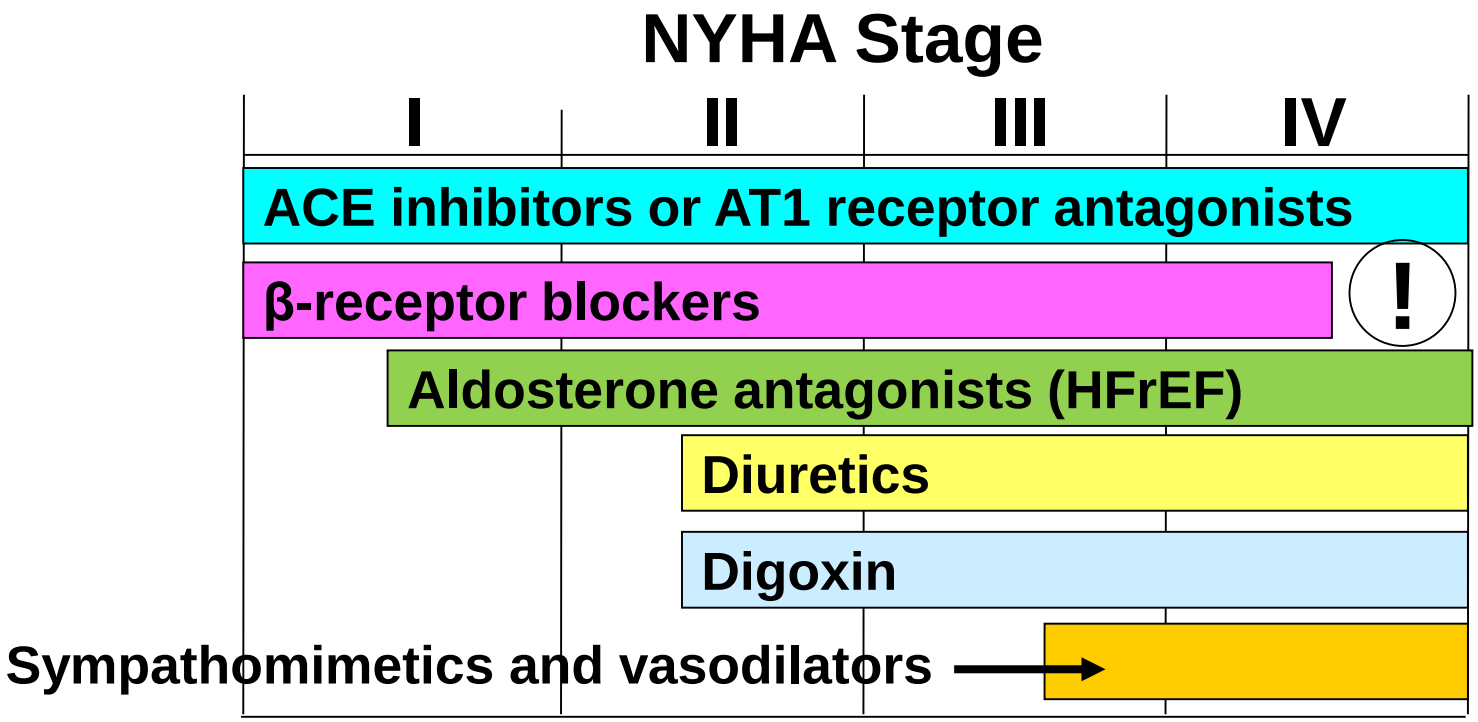
- Prevention and treatment of etiological factors: ischemic heart disease hypertension, arrhythmias, valvular disease, etc
- Diet: sodium restriction, moderate volume intake
- Physical activity to conform to clinical stage of HF

2. Drug treatment

3. Invasive therapy

- cardiac assist devices (CAD, LVAD)
- heart transplantation

TREATMENT STRATEGY OF HEART FAILURE ACCORDING TO NYHA STAGES



β-blockers

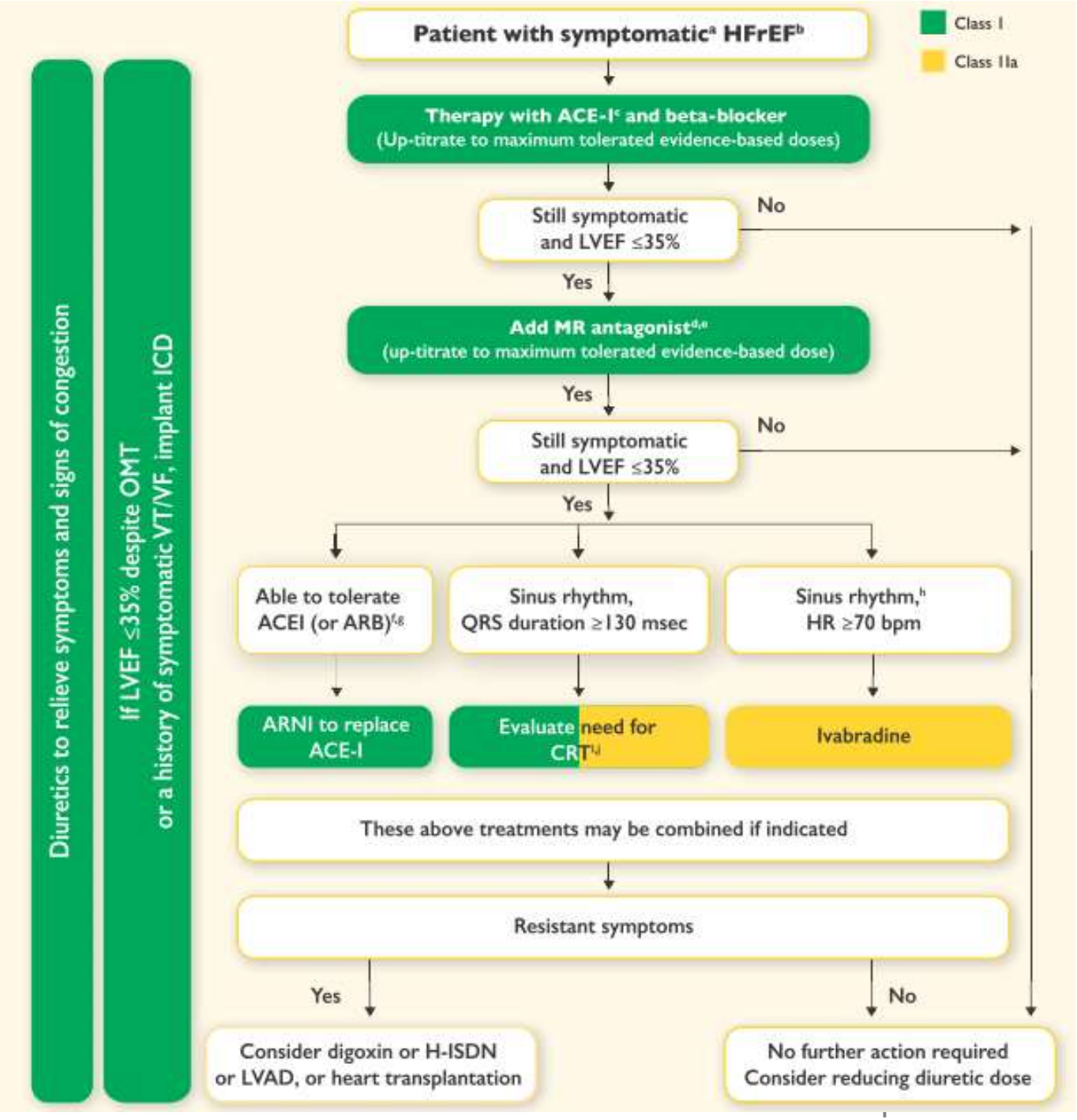
- mostly cardioselective, ISA-free agents (bisoprolol, metoprolol, nebivolol)
- small doses, titrated carefully
- attention in very severe HF!! !

Aldosterone antagonists

- in all advanced HF cases

TREATMENT STRATEGY OF HEART FAILURE (HFrEF)

(HFmEF or HFpEF – treat comorbidities)



DRUGS USED IN HEART FAILURE

- **ACE-inhibitors, AT_1-antagonists (ARBs)**
  - to decrease afterload, preload, remodelling process

  (Captorpil, enalapril etc… losartan, valsartan, irbesartan, etc…)
  - decrease mortality
- **β-blockers** - not all of them
  - alleviates sympathetic activation
  - decrease the risk of mortality – only if no atrial fibrillation is present

  (carvedilol, labetolol, metoprolol, bisoprolol, nevibolol)
- **Diuretics**
  - decrease preload (and afterload)
  - aldosterone antagonist decrease mortality
- **Venodilators**
  - decrease preload
  - nitrates + hydralazyn – decrease mortality
  - nesiritide – recombinant BNP
- **Positive inotropic drugs**
  - Cardiac glycosides → for systolic heart failure (LVEF<40%, NYHA III-IV)
  - Other positive inotropic drugs → for severe heart failure

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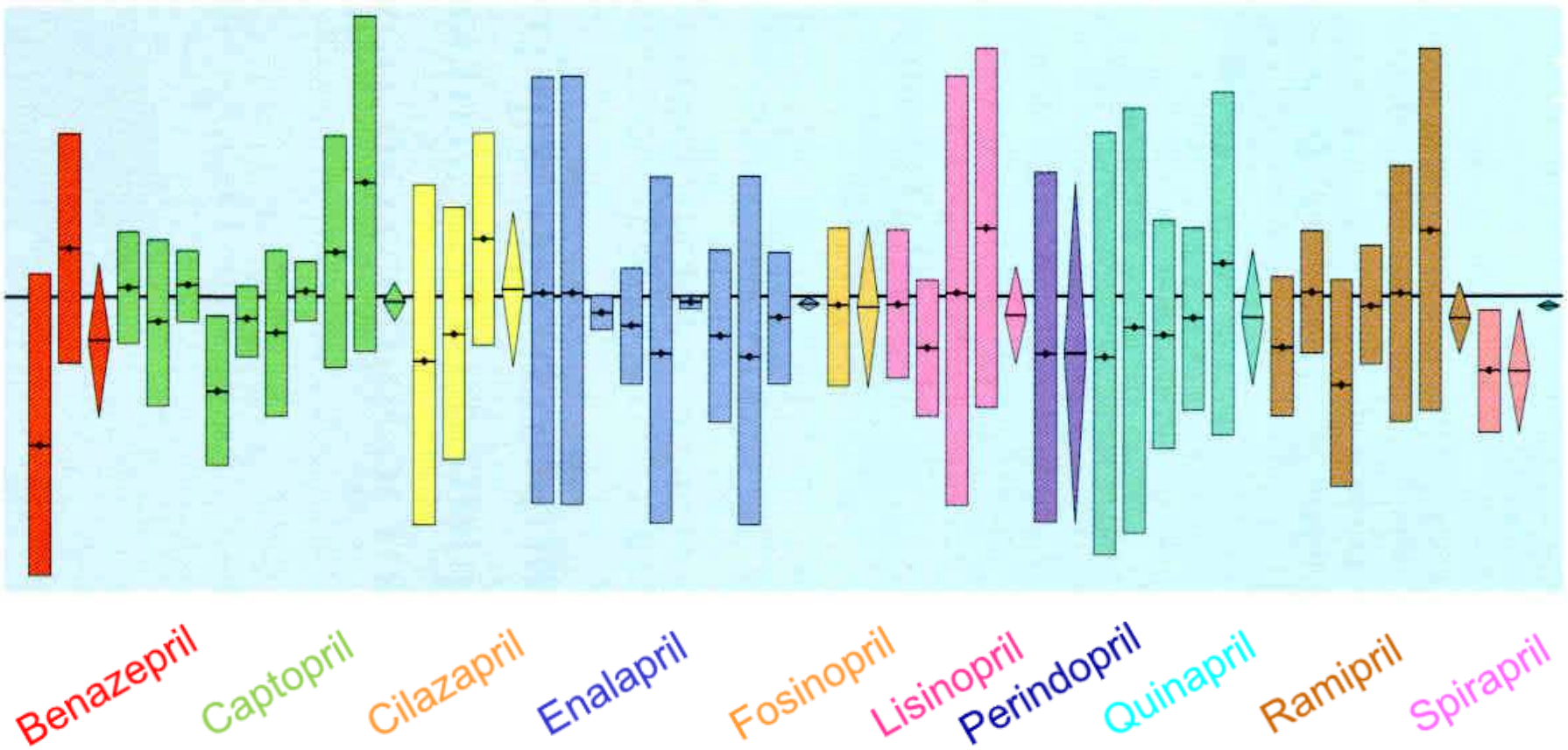
EFFECT OF ACE INHIBITORS ON SURVIVAL
META-ANALYSIS

Every ACE inhibitor improves survival in heart failure

(Eccles M et al.: BMJ, 316:1369, 1998)



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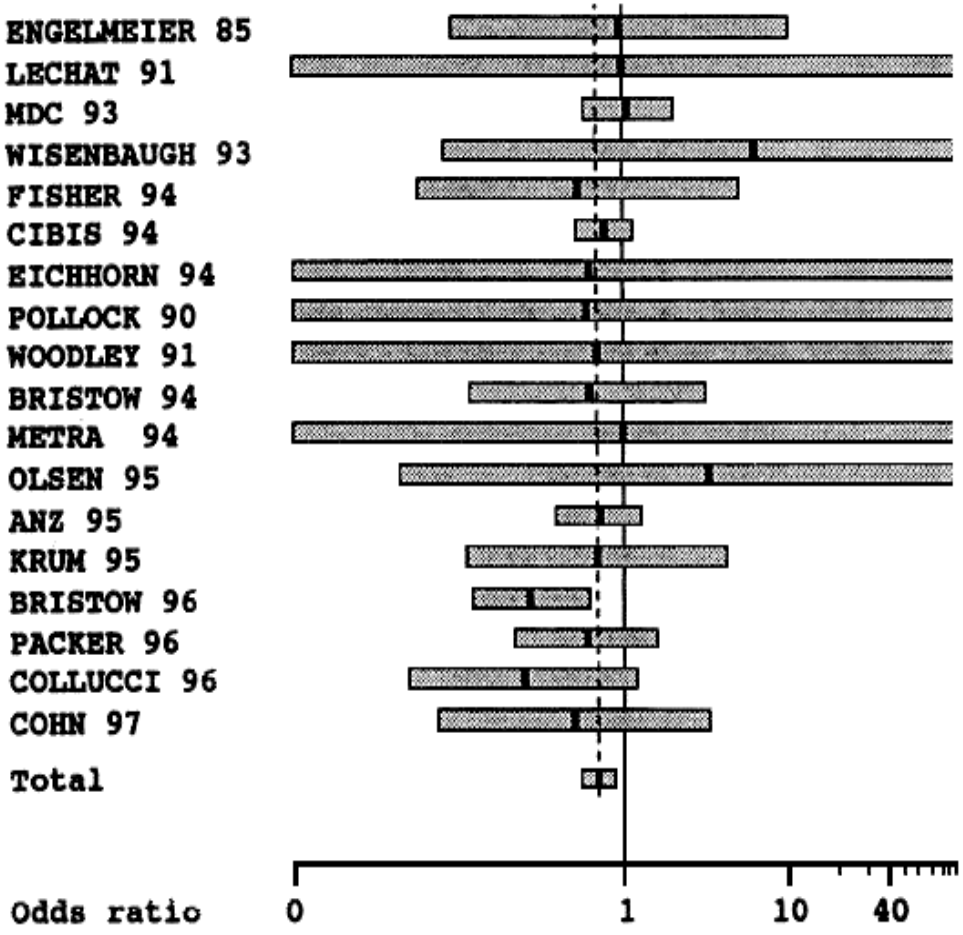
EFFECT OF β-RECEPTOR BLOCKERS
META-ANALYSIS

The administration of β-receptor blockers reduces the risk of mortalitity due to heart failure

Lechat et al.: Circulation, 98/1184, 1998



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DIURETIC TREATMENT IN HEART FAILURE

Effects on survival

- Diuretics themselves do not improve survival.
- Exception: aldosterone antagonists - inhibit hyperactive RAAS, increase survival

Effects on symptoms

- Supportive treatment improving the functional conditions

Strategy

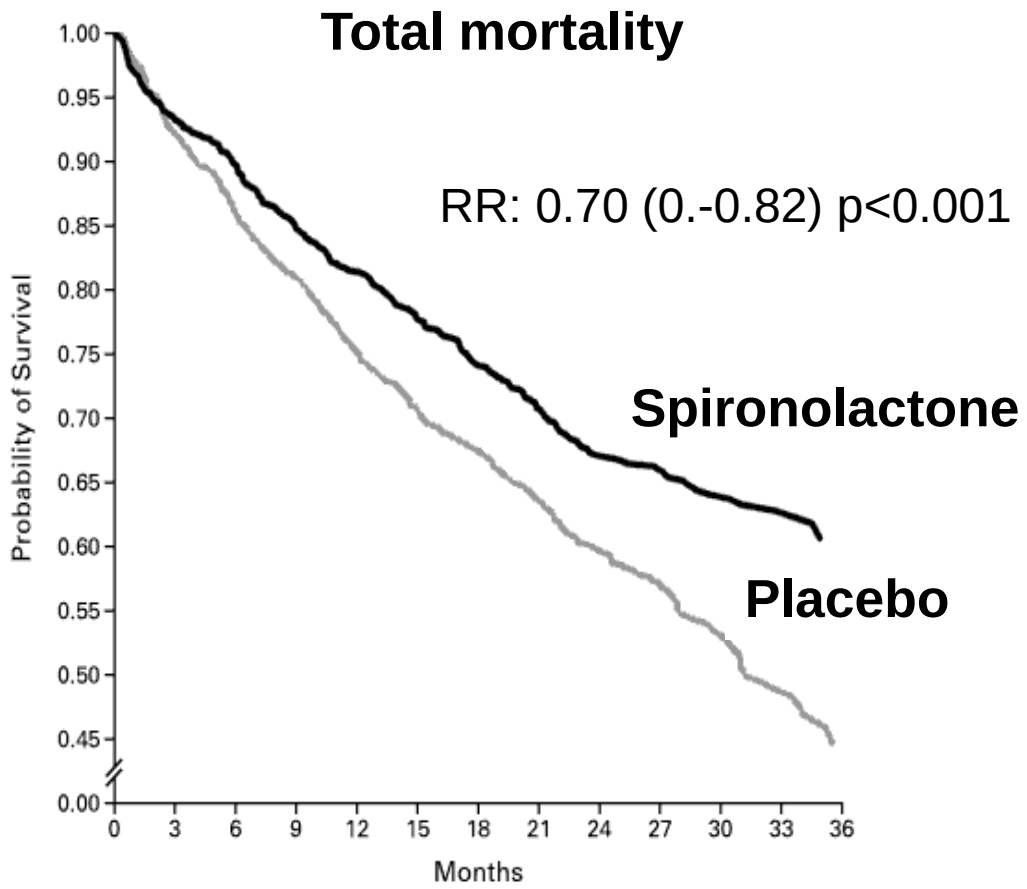
- In severe and acute heart failure – loop diuretics (Furosemide: 40 -120 mg/d; bumetanide 1-10 mg/d; torsemid 10-50-100 mg/d)
- In mild heart failure – thiazides or in combination with loop diuretics (Hydrochlorothiazide 25 mg/d, metolazon 2.5 mg/d)
- Hypokalemia prevention – loop diuretics combined with K^+-sparing diuretics (spironolactone, amiloride, triamterene)
- The titration of the dose of diuretics should be repeated at the introduction of ATII inhibitors,
- K^+-level monitoring

SPIRONOLACTONE IN SEVERE HEART FAILURE
META-ANALYSIS

The administration of spironolactone reduces mortality

Mineralocorticoide Receptor Antagonist (MRA)

Pitt et al.: NEJM, July, 1999



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VENODILATORS IN HEART FAILURE

Indication – Supporting therapy:

- Administered if symptomes persist even after reaching maximal tolerable doeses of ACEI/ARB+β-blocker+MRA combination therapy

Strategy

- Cases with increased preload, congestion
  - Nitrates → dilation of venules → reduced preload
- Cases with reduced cardiac output, hypertension
  - Hydralazyn → dilation of arterioles → reduced afterload
- Mixed cases (most often)
  - Combined nitrate and hydralazin therapy

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APPLICATION OF CARDIAC GLYCOSIDES

Indication

- Limited because
  - increased mortality
  - possible serious toxicity
  - newer agents are available
- Indicated only in severe heart failure (NYHA III - IV),
- Mainly in heart failure associated with sinus arrhythmia

Effects

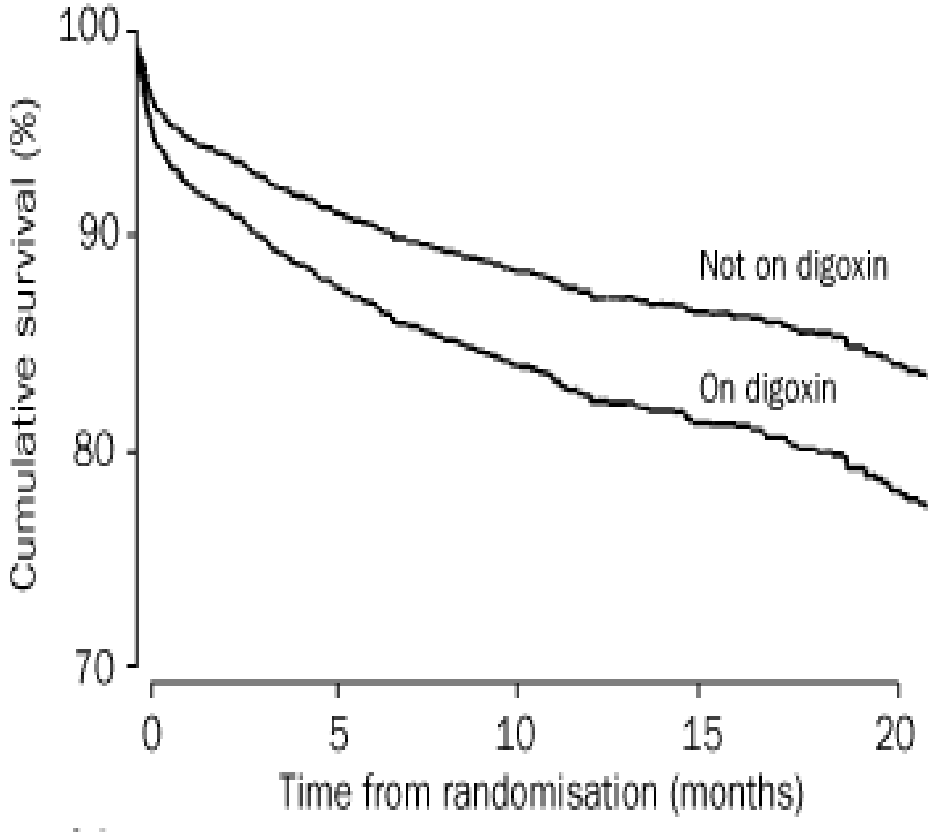
- Digoxin reduces mortality due to worsening HF, but increases mortality due to other cardiac causes (sudden cardiac death)
- From among the cardiac glycosides, digoxin is preferred due to its clinical pharmacological characteristics

DIGOXIN AND MORTALITY IN HEART FAILURE FOLLOWING MYOCARDIAL INFARCTION

In multivariate analysis digoxin is a significant predictor of overall mortality

Spargias et al.: Lancet, 354:391, 1999.

Cumulative survival



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Other positive inotropic drugs: β1 agonists

- IC Ca^{2+} ↑ → contractility ↑

- ***<u>Dobutamine:</u>***

- Positive inotropic effect (increase cAMP level)
- Less arrhythmogenic due to mild positive chronotropic effect
- Acute circulatory shock - i.v. short term use (tachyphylaxis)

- ***<u>Dopamine:</u>***

- Strong positive inotropic effect
- Renal vasodilation (D1 agonist)
- Acute circulatory shock, i.v.

Other positive inotropic drugs: PDE antagonists

- Inhibition of phosphodieterases - cAMP increases - IC Ca^{2+} increase – contractility increases + vasodilator („inodialator”)

Metilxanthin derivatives:

Theophyllin, aminophyllin

Bipyridine derivatives:

Amrinon, Milrinon: PDE3 antagonists

Side effect: thrombocytopenic, hepatotoxic, arrhythmogenic

Other, mixed effect: **Vesnarinon**

- weak PDE3 inhibitor, + inotropic and vasodilator (minimal negative chronotropic)
- strong inhibitor of K+ channels, weak activator of Na+ channels – increasing IC Ca2+, elongation of action potential plateau phase
- TNFa and IL-6 formation inhibitor

Only for acute treatment – increase mortality in chronic use!

Other positive inotropic drugs: Ca-sensitizers

- increases the Ca sensitivity of the myofibrills (tropinin C)

-„energy sparing” inotropic effect

- no arrhythmogenic effect,

- no effect on relaxation

(no breakthrough benefit – e.g. not approved in the USA)

• ***<u>Pimobendan</u>***

- also inhibits PDE

• ***<u>Levosimendan</u>***

- activates ATP-sensitive K^+ channels as well $\rightarrow$ venodilator

New developments in the treatment of heart failure

- **Coenzim Q10** – adjuct to specific treatment - decreases mortality
- **Nesiritide:** recombinant BNP – i.v. acute severe heart failure
- **ANP and urodilatin analogs**: carperitide, ularitide
- **Renin inhibitors**: aliskiren (antihypertensive drug)
- **Ivabradin** (anti-ischemic drug, its indications have been recently extended for HF)
- **Endotelin-1A and B receptor antagonists** (bosentan – pulmonary hypertension, macitentan, tezosentan)
- **Endotelin converting enzyme inhibitors**: phosphoramidon
- **ADH antagonists** („aquaretics”) – **Tolvaptan**
- **Serelaxin** – recombinant human relaxin-2 – acute severe heart failure

Ivabradine in chronic heart failure

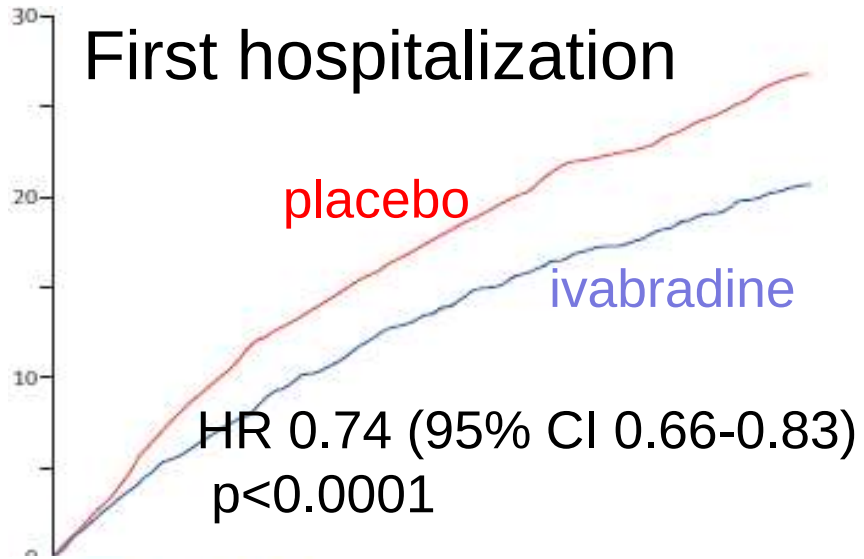
SHIFT study

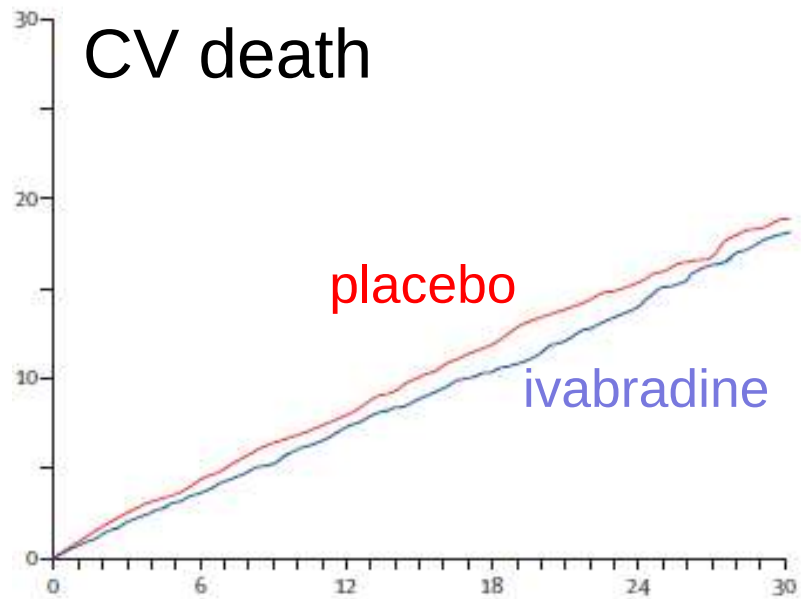
Swedberg K. et al. Lancet 875-883. 2010

Ivabradine is a spcific inhibitor of I_f current in the sinoatrial node.
No other action.

Main side effect of ivabradine:

- bradycardia
- visual disturbance





New developments in the treatment of heart failure

• **NEP (neutral endopeptidase - neprilysine) inhibitors:**

- increase ANP, BNP → enhanced diuresis, anti-remodelling effect

- candoxatril, omapatrilat (severe angioedema – not on the market)

- **sacubitril + valsartan combination** (LCZ696) – first product in decades that is more effective than enalapril and safe - **PARADIGM-HF trial**
http://www.nejm.org/doi/full/10.1056/NEJMoa1409077

•**SGLT2 inhibitors**

- Caridoprotective effect in T2DM (empaglifonize - EMPA-REG OUTCOME, canaglifozine – CANVAS Program)

•**Iron supplementation?**

- i.v iron improved heart function and quality of life

(CONFIRM-HF + FAIR-HF trials)

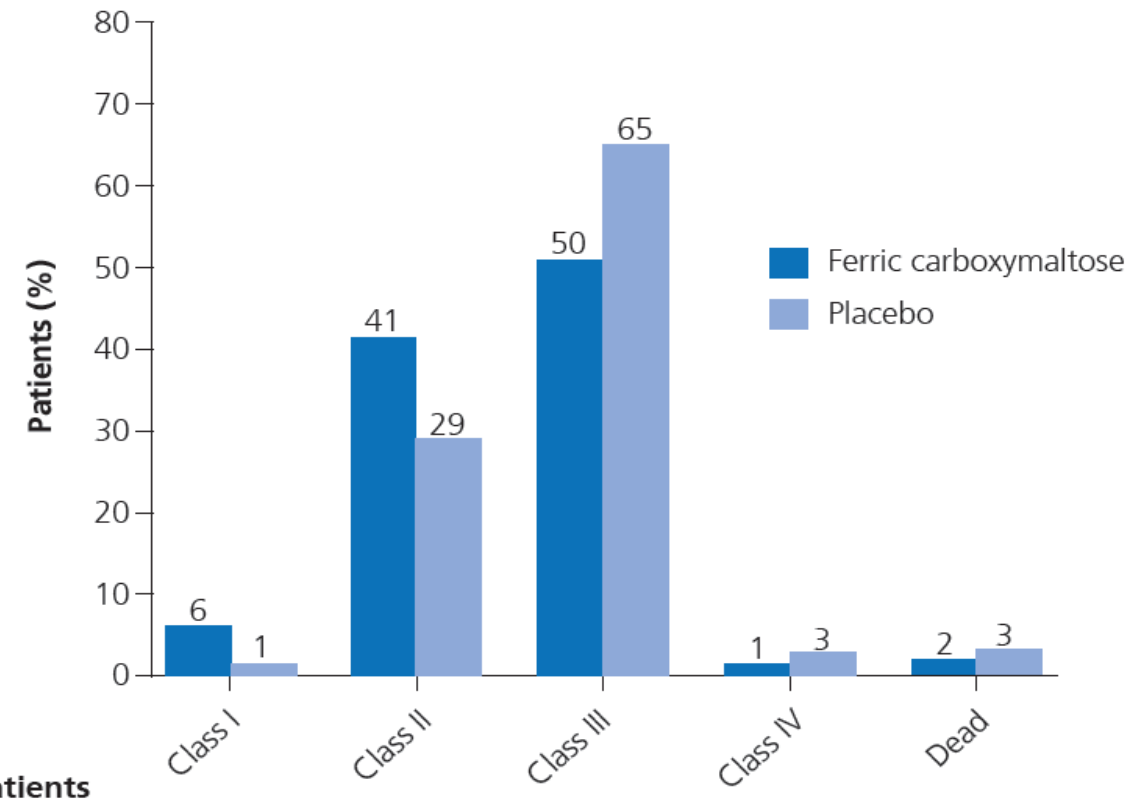
- more than 40% of HF patients have iron deficiency

Iron Supplementation - The FAIR-HF Trial

Ferric carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure

Anker SD et al, N Engl J Med. 2009;361:2436–2448.

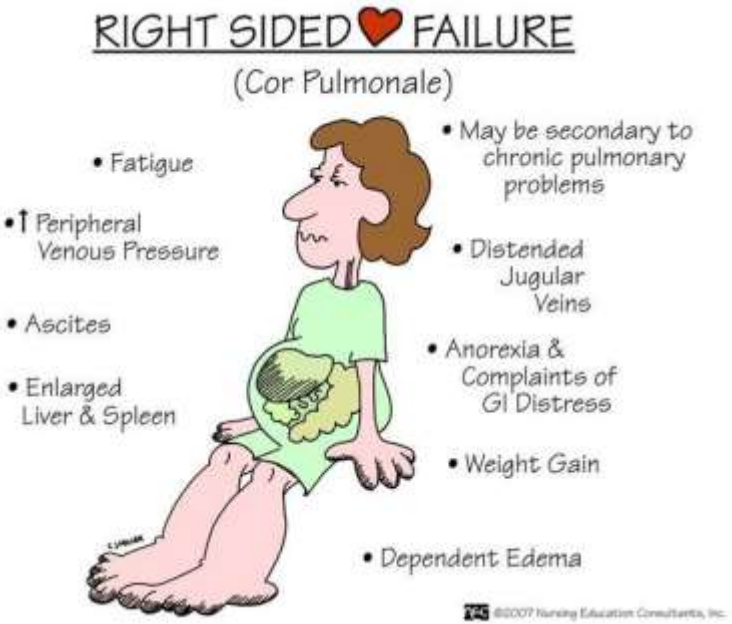
B: NYHA Functional Class at Week 24



No. of patients	Class I	Class II	Class III	Class IV	Dead
Ferric carboxymaltose	17	121	148	3	5
Placebo	2	43	97	4	4

Right heart failure – pulmonary hypertension

- **Pathophysiology:**
  - Secondery pulmonary hypertension (pulmonary embolization)
  - Valve dysfunction
  - Pericardial diseases



- **Signs and Symptoms - dyspnoea**, dilated jugular vein, ascites, epigastrial discomfort or pain, edema, auscultation signs, ECG changes

- **Therapy:**
- Supportive therapy: diuretics, digoxin, anticoagulants and oxygen
- Vasoreactive cases – relatively large dose Ca channel blocker (nifedipine, diltiazem)
- Specific therapy:
  - Prostanoids – pl. braprost, iloprost
  - Endotelin receptor anatagonists (ERA) – ambisertan, bosentan, macitentan
  - targeting the NO-cGMP pathway: PDE5 ihibitors – sildenafil, tadalafil; guanilate-cyclase stimulators – riociguat, NO inhalation – pulmonary hypertension

Acute heart failure

Definition

- rapid onset or worsening of symptoms and/or signs of heart failure
- first/de novo occurence or sudden decompensation of chronic heart failure

Most common causes

- acute myocardial dysfunction (ischaemic, inflammatory or toxic)
- acute valve insufficiency
- pericardial tamponade

Classification

- periferial perfusion: warm vs. cold
- congestion: dry vs. wet
- worst prognosis: cold and wet

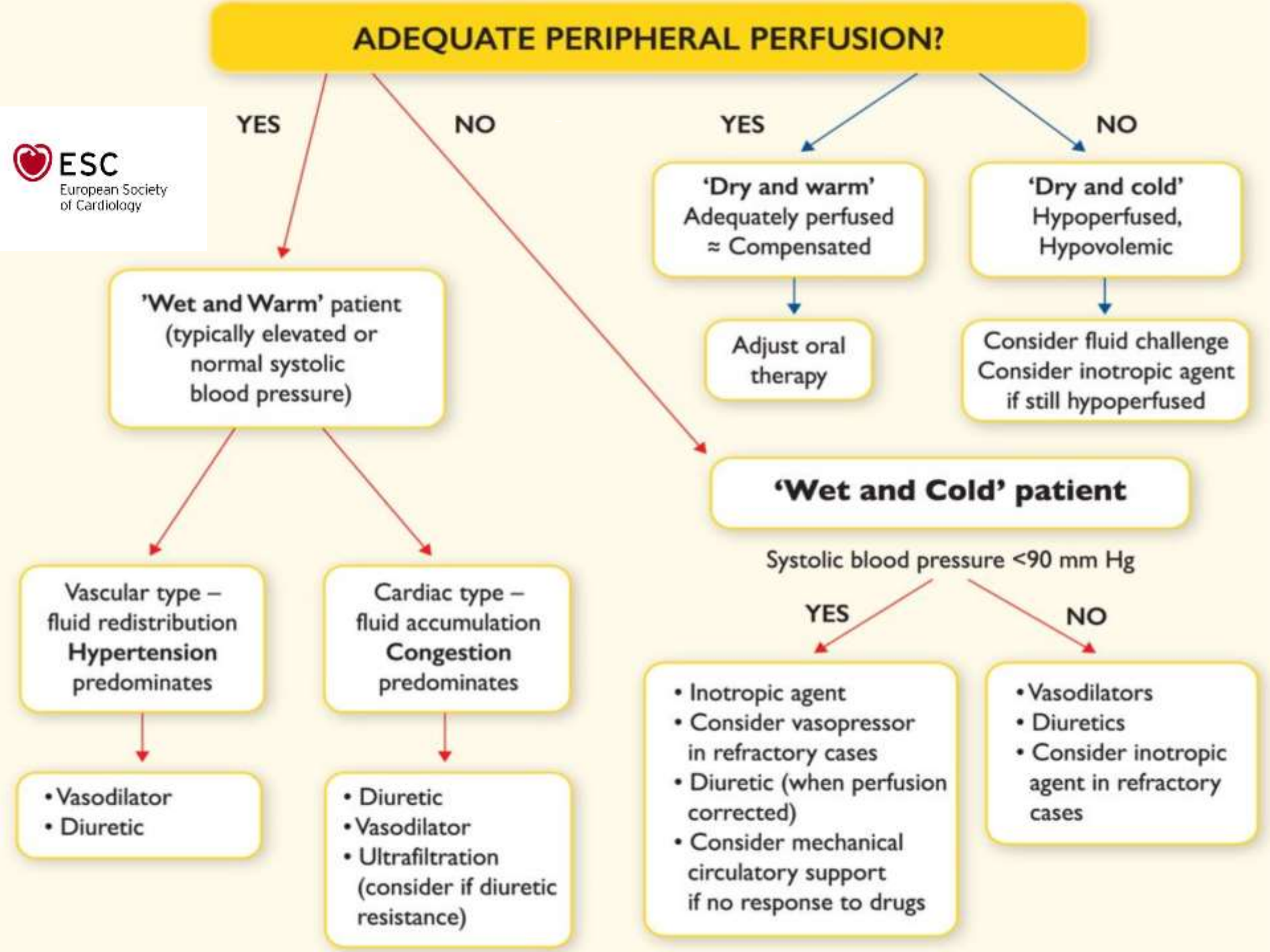
Acute heart failure

Pharmacotherapy

- Management of the cause (arrhythmia, hypertension, acute MI etc.)
- „Dry and warm” type: edema, congestion – **iv. loop diuretics** + opiates (in severe dyspnea, decreases respiratory distress)
- „Cold and wet” type: Circulatory support
  - *SBP < 90 mmHg* – inotropic agent without vasodilator effect – **dobutamine**
    - Vasopressor support in hypotonia, diuretics in edema
    - Mechanical circulation support – refracter cases
  - *SBP > 90 mmHg* – vasodilators: **nitrates** (nitroglycerin, isosorbide dinitrate, sodium nitroprusside)
    - Human BNP analogue (nesiritide)
    - Inotropic agent can be considered

Contraidicated:

Acute β-blocker administration, ACE-inhibitors/ARB, Ca-antagonists


ADEQUATE PERIPHERAL PERFUSION?
YES
NO
YES
NO
ESC
European Society of Cardiology
'Dry and warm'
Adequately perfused
≈ Compensated
'Dry and cold'
Hypoperfused,
Hypovolemic
Adjust oral therapy
Consider fluid challenge
Consider inotropic agent if still hypoperfused
'Wet and Warm' patient (typically elevated or normal systolic blood pressure)
'Wet and Cold' patient
Systolic blood pressure <90 mm Hg
YES
NO
Vascular type – fluid redistribution
Hypertension predominates
Cardiac type – fluid accumulation
Congestion predominates
• Vasodilator
• Diuretic
• Diuretic
• Vasodilator
• Ultrafiltration (consider if diuretic resistance)
• Inotropic agent
• Consider vasopressor in refractory cases
• Diuretic (when perfusion corrected)
• Consider mechanical circulatory support if no response to drugs
• Vasodilators
• Diuretics
• Consider inotropic agent in refractory cases