Heart failure - definition

- **a condition when the heart cannot satisfy the circulatory needs of the body despite a sufficient blood supply to the heart**

- vital organs chronically suffer from inadequate blood perfusion
- dysfunction of the myocard of ventricles due to various diseases
- a leading cause of mortality and morbidity

> 23 millions of patients with heart failure worldwide

3,6 millions of newly diagnosed patients in Europe EVERY YEAR

Chronic heart failure (CHF)

- symptoms: subjective feeling of the patient
  dyspnoe + fatigue → limited exercise tolerance
- signs: objective indicators that can be noticed by other people
  fluid retention → pulmonary congestion and peripheral oedema
- consequences: the inability of the heart to meet the metabolic demands of peripheral tissues results in tissue hypoperfusion and inadequate delivery of oxygen

Heart failure - symptoms

- dysfunction of myocardial function
- disturbance of neurohumoral regulation
- intolerance of applied load
- the most common symptoms: dyspnoe, shortness of breath, fluid retention, oedema, fatigue
- shortening of life
- terminal stage of cardiovascular diseases

Heart failure - terminology

- chronic heart failure
  - most common
- acute heart failure
  - de novo
  - decompensation of the CHF
  - with lung oedema
  - cardiogenic shock
  - HT crisis
  - right/left ventricle failure

Homeostatic responses to impaired cardiac output

early responses - beneficial ☺
later these responses: detrimental ☹

Activation of

- RAAS (angiotensin II, aldosteron)
  due to reduced renal blood flow
- sympathetic nervous system (noradrenalin) -> increased output
- vasopressin (ADH), endothelin, cytokines

Epidemiology of CHF

- prevalence
  - 1 -2% overall
  - 6-10 % in elderly population
- morbidity
  – one of the most common cardiac causes of hospitalizations and outpatient visits
- mortality
  – 50% in 5 years in general
  – 50% in 1 year in severe cases

Classification of CHF

- **Which side of heart is affected**
  - **Left** (more common, pulmonary congestion)
  - **Right** (hemostasis in peripheral vessels - oedema)
- **Which heart function is affected**
  - **Systolic** (↓ contraction and EF, dilated LV)
  - **Diastolic** (↓ relaxation, preserved EF)

NYHA Functional Classification		ACC–AHA Stages of Heart Failure	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

* The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al.[8] The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.[12]

Drugs for CHF

NYHA I	NYHA II	NYHA III	NYHA IV
ACEI/ARB	ACEI/ARB	ACEI/ARB	ACEI/ARB
B-blocks	B-blocks	B-blocks	B-blocks
	Diuretics	Diuretics	Diuretics
		Digoxin	Digoxin
			Inotropics i.v.
			LVAD

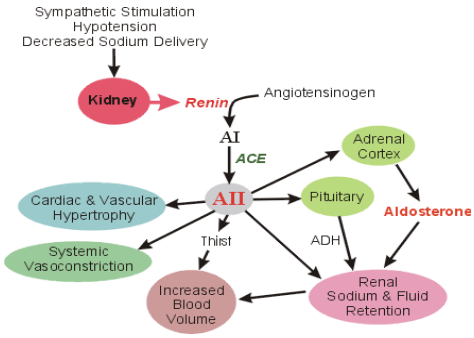
Therapeutic options in CHF

- ACE inhibitors/ ARB/ renin inhibitors / BAR
- Beta blockers
- Diuretics
- Digoxin
- Dobutamine
- PDE-III inhibitors (milrinone)
- Other vasodilators
- Amiodarone
- (Ivabradine)
- Anticoagulants, antiaggreg.

1A. Angiotensin-converting enzyme inhibitors

- 1st-line treatment in CHF
- reduce risk of developing HF in high-risk patients (previous MI, vascular disease or DM)
- before the start of therapy reduce doses of diuretics (ev. withdraw); do not use kalium sparing diuretics appart from spironolactone
- start low, titrate to target (gradually increase the dose, control blood pressure, renal functions (creatinine), ions)
- aim – reach maximum of the tolerated dose

- improvement:
  - mortality
  - morbidity
  - exercise tolerance
  - left ventricular ejection fraction



1A. Angiotensin-converting enzyme inhibitors

I:

- to all CHF patients with left ventricular systolic dysfunction unless contraindicated
- use with diuretics in patients with recent or current history of fluid retention

AE:

- dry irritating persistent cough (10-15 %)
- hyperkalemia (aldosteron reduced)
- angioedema 0,1 – 0,2 %)
- fetal toxicity

1A. Angiotensin-converting enzyme inhibitors

captopril, enalapril, lisinopril, ramipril, fosinopril, quinapril, trandolapril, perindopril Lowering the afterload

ACEi	Dosing
captopril	**3 x 12,5 - 50 mg**
enalapril	**2 x 2,5 - 10mg**
ramipril	**1x 2,5-10 mg**
lisinopril	**1 x 2,5- 20 mg**
trandolapril	**1 x 2-8 mg**
perindopril	**1 x 4-8 mg**

1B. Angiotensin Receptor AT-1 Blockers (ARB)

- competitive antagonists of angiotensin II (AT-1 receptors)
- no inhibition of ACE, bradykinin (no cough)
- recommended for routine administration to symptomatic and asymptomatic patients with **LVEF ≤ 40% who are intolerant to ACEi**

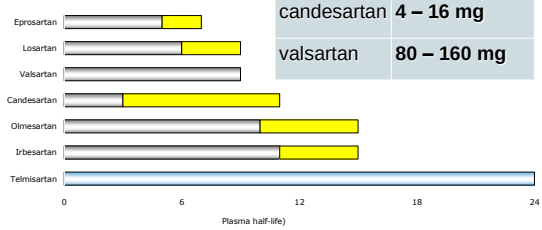
for reasons other than hyperkalemia or renal insufficiency (usually cough)

ARB: candesartan, valsartan, *losartan* Lowering the afterload
BRA: spironolactone, eplerenone Lowering the afterload

- LVEF – left ventricular ejection fraction

1B. ARBs – „sartans“

ARB drug	dose
losartan	**25 – 100 mg**
candesartan	**4 – 16 mg**
valsartan	**80 – 160 mg**



1C. Renin inhibitors

(aliskiren)

MoA: selective direct inhibitory action on the renin enzyme

- reduces plasma renin activity by 50-70 %

D: once daily, 150 – 300 mg orally

I: **essential HT only**, monotherapy or combination with ACEi

BUT avoid combinations **with ARBs or ACEi** in patients with DM, kidney impairment, hyperkalemia

1D. Aldosterone antagonists (BRA)

eplerenone, spironolactone (blockers of receptors for aldosterone)
Lowering the afterload

2. Beta blockers

- act primarily by inhibiting the sympathetic nervous system
- competitive inhibition on β adrenoceptors
- anti-arrhythmic properties
- anti-oxidant properties
- Lowering the speed, energy saving

  - **competitive antagonists** (intrinsic activity = 0)
    OR
  - **partial agonists** (ISA - intrinsic sympathomimetic activity)

2. Beta – blockers

Cardiac effects

- decrease contractility (neg. inotropy)
- decrease of heart rate (neg. chronotropy)
- decrease conduction velocity (negative dromotropy)

CARDIOPROTECTIVE EFECT

- (saving myocardial effort

=> decrease of O_2 consumption)

2. Beta – blockers - organ functions

- cardiovascular system : negative chronotropic and inotropic effect => decrease of the blood pressure
- renal system: decrease of the renin secretion
- respiratory system: bronchospasm
- eye: decrease of the intraocular pressure
- metabolic effects: reduction of glycogenolysis and lipolysis

2. Beta – Blockers - classification

- **non-selective (**b**1 + **b**2) propranolol, metipranol**
- **(cardio)selective (**b**1)** metoprolol, bisoprolol, **betaxolol, atenolol**
- **non-selective with ISA (**b**1 + **b**2) pindolol**
- **(cardio)selective (**b**1) with ISA acebutolol, celiprolol**
- **combining** α **+** β **blockade =** carvedilol**, labetalol**
  β **-blockers of IInd generation**

2. Beta – blockers – dosing in CHF

- START LOW, GO SLOW!
- start at low dose and monitor for bradycardia
- carvedilol, bisoprolol and metoprolol are the most commonly used B-B

ZOK – Zero Order Kinetics

B-B	Initial dose	Target dose
Bisoprolol	1x1,25mg	1x10mg
Carvedilol	2x 3,125 – 6,25 mg	2x 25 mg
Metoprolol ZOK	1x 12,5 – 25 mg	1x 200 mg
Nebivolol	1x 1,25 mg	1x 10 mg

2. Beta – blockers – AE:

- fuid retention (→ worsening CHF)
- hypotension (→ fatigue)
- bradycardia (→ fatigue)
- slow AV conduction (AV block)
- bronchoconstriction (non- selective)

3. Diuretics

- decreasing the extra cellular volume
- useful in reducing the symptoms of volume overload (dyspnea, oedema) recommended in patients with congestion
- decreasing the venous return
- have not proved benefitial effect on mortality

- Lowering the preload
- Thiazides: HDCHT, CHLTH, INDA
- Loop diuretics: furosemid, torasemid
- Kalium saving diu: spiro, eple, amilo, triam

3. Diuretics

Loop diuretics **furosemide**
- the most effective – more intense and shorte diuresis
- commonly used in severe forms CHF
- combination with ACEi, spironolactone

Thiazides
- effective in mild cases only
- more gentle and prolonged diuresis
- combination with loop diuretics
- Less effective with a reduced kindey function

hydrochlorothiazide, indapamide

3. Diuretics – AE:

- loop diuretics and thiazides cause hypokalemia
- potassium sparing diuretics help in reducing the hypokalemia induced by loop d. and thiazides

risk of dehydration → hypovolemia → renal dysfunction

4. Cardiac glycosides

Digitalis purpurea,
Digitalis lanata

- **digoxin** comes from foxgloves and related plants - containing several cardiac glycosides
- drug of the 3rd choice - after ACEi/ARBs, after B-B ev. diuretics

inhibition of Na+/K + ATPase pump increases intracellular sodium concentration -> increased level of intracellular calcium ions

4. Cardiac glycosides - digoxin

- increase the refractoriness of AV node thus decrease ventricular response to atrial rate ….
- positive inotropic effect (↑contractility)
- negative chronotropic (↓heart rate)
- negative dromothropic (↓conduction)
- positive bathmotropic (decreased depolarisation treshold)
- Dose 1 x 0,125-0,25mg
- to reach plasmatic concentration 0,55 - 0,9 ng/ml = 0,6-1,1 nmol/L

4. Cardiac glycosides - digoxin

- absorbtion from GI 60-75%
- albumin binding 20-40 %
- T 1/2 = 36 hours
- liver metabolization app. 20 %
- renal elimination app. 75 %
- TDM (0,5-0,9 ng/ml = 0,6-1,1 nmol/l)

4. Cardiac glycosides – digoxin AE:

- arrhythmias
  - AV bloc
  - ectopic and re-entrant cardiac rhythms
- GIT side effects
  - anorexia, nausea, vomiting
- neurological complications
  - visual disturbance, disorientation, confusion

Therapy of digoxin overdose:

- plasma levels above 2,3 ng/ml
- stomach wash-out, carbo adsorbens
- continuous measurement of ECG and serum electrolytes
- Kalii chloridum 4-10 g/day orally or i.v. infus.
- therapy of arrhythmias phenytoin, resp. prokainamide, (atropine/B-B if there is no bradycardia)
- th. of hyperkalemia: glucose infus., insulin, hemodialysis

5. Other cardiac inotropes

dobutamine - beta-1 agonist

- increases contractility and cardiac output

milrinone, (amrinone)

- phosphodiesterase III inhibitors (responsible for degradation of cAMP)
- increase of the myocardial contractility

levosimendan – Ca sensitizer

- sensitisation of cardiac muscle to calcium (also in vascular smooth muscle)

I: severe hearth failure, cardiogenic shock

Targets of CHF treatment

- **Mortality reduction** (evidence based)
  - – ACEI
  - – AT1 blockers
  - – aldosteron antagonists – spironolactone
  - – beta-blockers
- **Quality of life** (mortality reduction not proved)
  - – diuretics
  - – digoxin

Arrhythmias in CHF

- Sinus bracykardia
- Sinus tachycardia
- Atrial tachycardia/ flutter/ fibrilation
- Ventricular arrhythmias
- Atrioventricular block

Atrial fibrillation

- most common arrhythmia in CHF
- risk of trombo-embolic complication (stroke)
- **therapy in REF (systolic HF)**
  - B – blocker
  - digoxin (alternative or addition to BB)
  - amiodarone (alternative monotherapy or addition to BB or digoxin)
  - AV node ablation and pacing
- **therapy in PEF (diastolic HF)**
  verapamil/ diltiazem

- Profylaxis of trombembolism

Antiarrhythmic agents - general principles of use

- may predispose to ventricular arrhythmias
- their role is declining
- rising importance of surgical treatment (ICD – implantable cardioverter defibrilator, RFA – radiofrequency ablation)
- many interractions with non- cardiac drugs – enhancing arrythmogenic potential (makrolides, quinolone antibiotics, diuretics
- K+ channel blockers prolong QT interval (amiodarone, sotalol)

- trend: surgical and mechanical therapy of arrhythmias in CHF

ivabradine

- MoA: reduces the heart rate via specific inhibition of the I_f channel
- selective decrease in rate without loss of contractility
- I_f is a mixed Na^+–K^+ inward ionic current important for regulating pacemaker activity in the sinoatrial (SA) node
- recommended in patients with heart frequency above 75/min
- treatment of congestive heart failure without decreasing the ejection fraction
- with heart failure of ischemic or non-ischemic etiology, NYHA class II or class III, IV, with or without diabetes, and with or without hypertension
- do not combine with verapamil and dilthiazem
- risk of atrial fibrilation

amiodarone

- reduction of mortality by 30 %
- long T ½ (40 – 50 days)
- common ADRs: depend on the dose/duration of its use
  - **lung fibrosis**
  - **thyreopathy**
  - **optic neuritis,** corneal deposits
  - hepatotoxicity
  - arrhythmogenic effect
  - alveolitis
  - skin changes, phototoxicity

verapamil, diltiazem

- non-dihydropyridine Ca^{++} channel blockers
- reduction of heart rate
- reduction of AV conduction
- **CI: do not use** with B blockers, digoxin, atrioventricular blockers
- common drug-drug interactions - inhibition of CYP450

Antiarrhythmic agents

Vaughan-Williams classification

	Active agents	Clinical use	MoA
Class I a	Prajmalin	Limited use	Interfere with Na+ channel / effects on cardiac potentials
Class I b	Lidocain	Ventricular tachycardia	
Class I c	Propafenon	Atrial fibrilation, reccurent tachyarrhythmias	
Class II	B –blockers (metoprolol, atenolol	Tachyarrhythmias	decrease conduction through the AV node
Class III	Amiodaron, Sotalol Dronedaron Ibutilid	Vetnricular tachycardia Atrial fibrilation - the most effective AA	K+ channel blocker, prolong repolarisation (QT int.)
Class IV	Ca channel blockers	Atrial fibrilation - rate reduction Paroxysmal supraventricular tachycardia prevention	Ca++ channel blocker
„Class V"	Digoxin		
	Adenosin	Supraventricular ventricular tachy	Slow AV conduction