CHRONIC HEART FAILURE

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Definition

- **Heart failure is 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
- It is a leading cause of mortality and morbidity

Epidemiology

- Prevalence
  - 1 -2% overal; 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

A growing epidemy

- 4.7 million symptomatic patients, estimated 10 million in 2037
- **Incidence:** About 550,000 new cases/year
- More deaths from heart failure than from all forms of cancer
- **Prevalence** is 1% between the the ages of 50 – 59, progressively increasing to >10% over age 80
- $30 billion/year (5% to 7% of total health care cost)

Main manifestation of CHD

- **Symptoms:** dyspnea + fatigue → limit exercise tolerance,

- **Signs:** Fluid retention → pulmonary congestion and peripheral oedema,

Causes of CHF

- Coronary Artery Disease (CAD) – 2/3
- Hypertension (HTN)
- Cardiomyopathy (Idiopathic dilated cardiomyopathy - IDC)
- Valve disease (mitral, aortal)

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)

Forms of Heart Failure

Systolic dysfunction

– Pumping problem

– More common

– Common cause: CAD

– Reduced ejection fraction (REF) < 40%

Diastolic dysfunction

– Filling problem

– Less common

– Common cause: HTN

– Preserved ejection fraction (PEF)

STAGE	DISABILITY
CLASS 1 MILD	No symptoms Can perform ordinary activities without any limitations
CLASS 2 MILD	Mild symptoms - occasional swelling Somewhat limited in ability to exercise or do other strenuous activities
CLASS 3 MODERATE	Noticeable limitations in ability to exercise or participate in mildly strenuous activities Comfortable only at rest
CLASS 4 SEVERE	Unable to do any physical activity without discomfort Some HF symptoms at rest

Homeostatic responses to impaired cardiac output

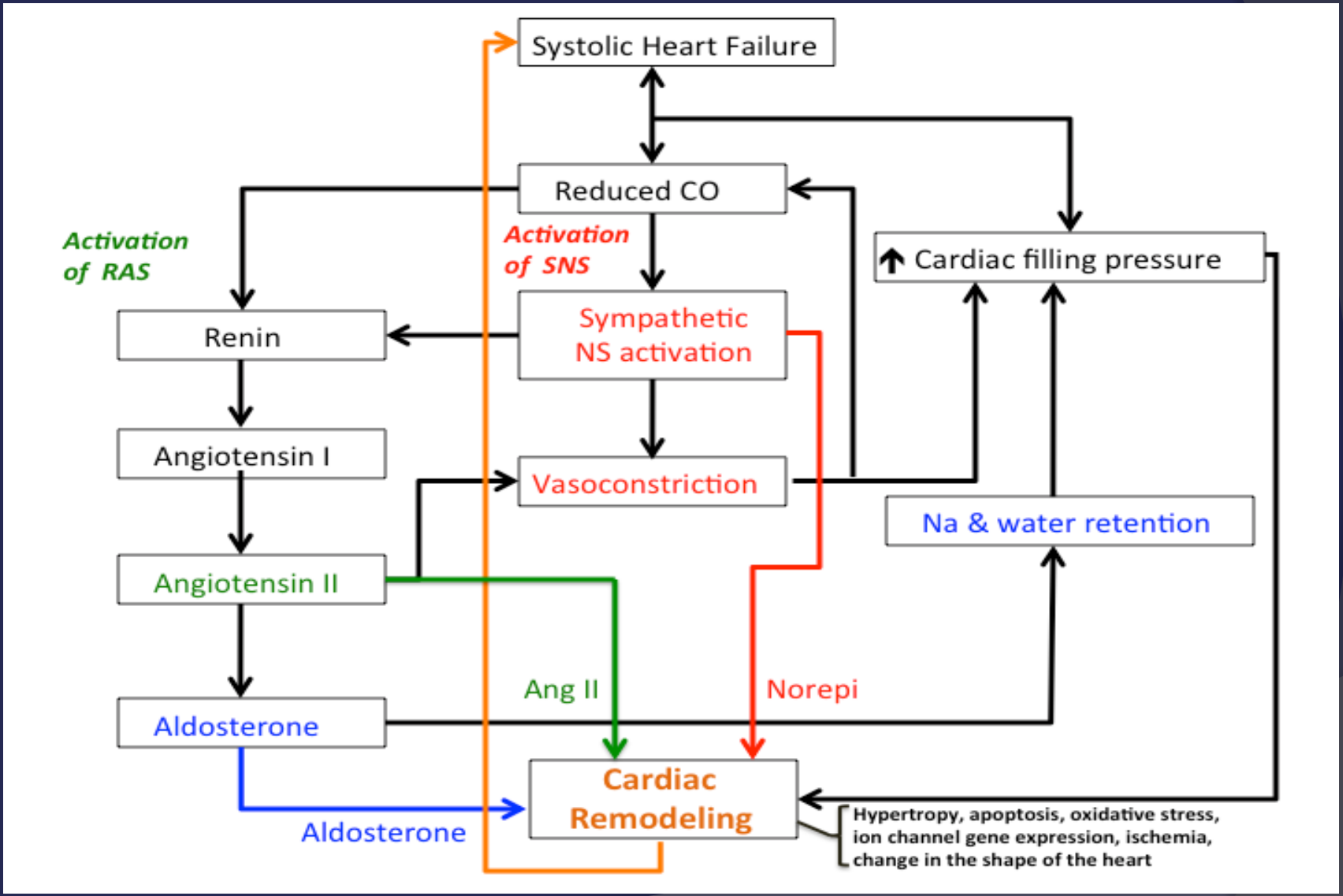
ACTIVATION of:

- Renin-angiotensin-aldosterone system
  (angiotensin II, aldosteron) due to reduced renal blood flow
- Sympathetic nervous system (noradrenalin)
  – increased output
- Vassopresin (ADH), Endothelin, Cytokines

Early responses - Beneficial

Later these responses: Detrimental

Pathofysiology of heart failure



Drugs for CCF

1. **ACE Inhibitors/ARB/ renin inhibitors**
2. **Beta blockers**
3. **Diuretics**
4. **Digoxin**
5. **Other Cardiac Inotropes –**
6. **Dobutamine, Milrinone**
7. Other vasodilatators

1A. Angiotensin-converting enzyme inhibitors

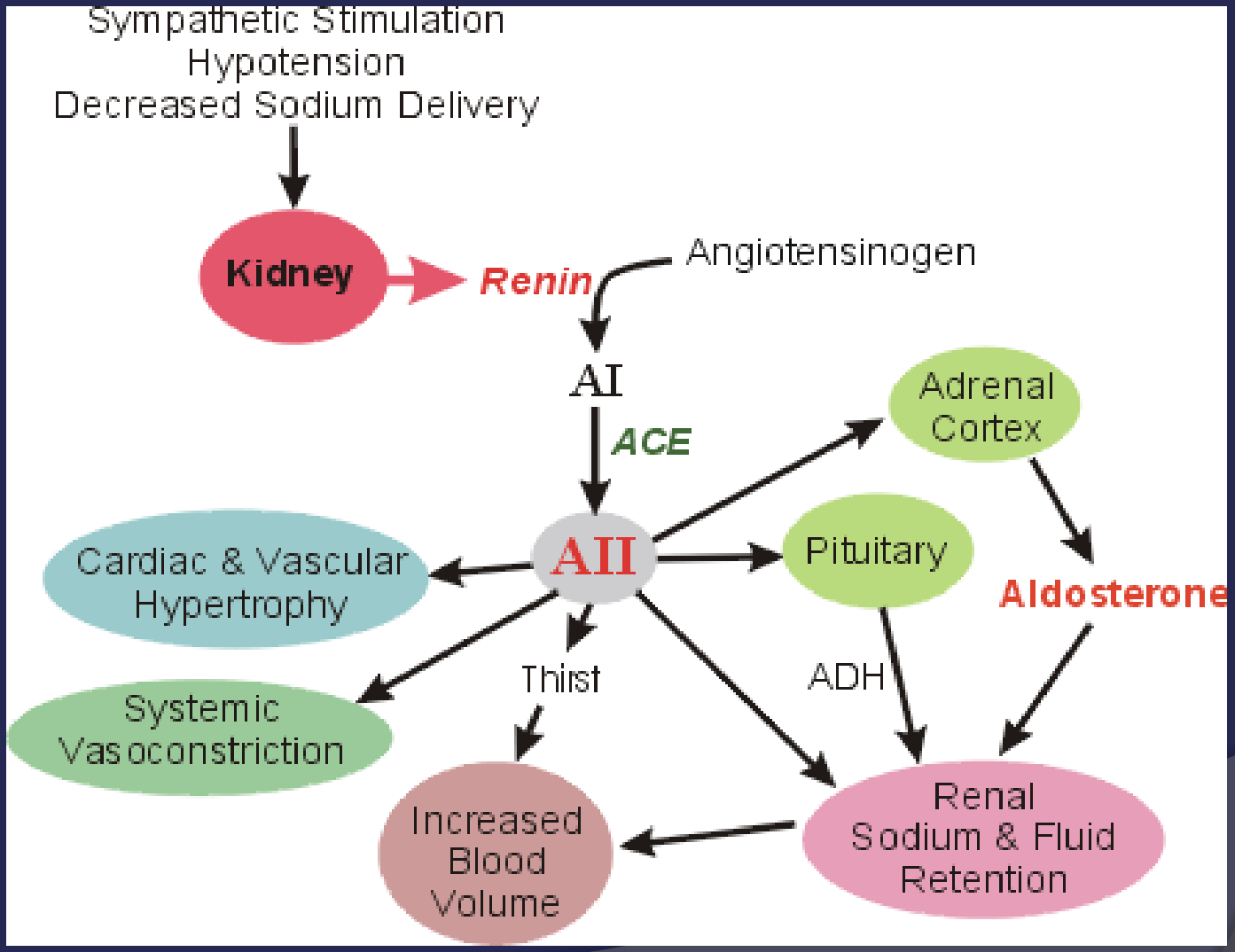
ACE inhibitors improve

- mortality
- morbidity
- exercise tolerance
- left ventricular ejection fraction.

1A. ACE inhibitors

- First-line treatment in CHF
- Beneficial across all functional classes of HF
- Reduce risk of developing HF in high-risk patients (previous MI, > 55 y.o. with vascular disease or DM)
- Start low, titrate to target (doses shown effective in clinical trials)

RAAS – target of ACEI action



Practical issues with ACEI - 2

Initial and target doses:

- Captopril: 6.25 mg tid target: 50 mg tid
- Enalapril: 2.5 mg bid target: 10-20 mg bid
- Lisinopril: 2.5-5 mg qd target: 20-40 mg qd
- Ramipril: 1.25-2.5 mg qd target: 10 mg qd
- Fosinopril: 5-10 mg qd target: 40 mg qd
- Quinapril: 10 mg bid target: 40 mg bid

ACEI – adverse events

- Dry irritating persistent cough (10-15 %)
- Hyperkalemia (aldosteron reduced)
- Angioedema 0,1 – 0,2 %)
- Fetal toxicity

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

- Competitive antagonists of Angiotensin II (AT-1 receptors).

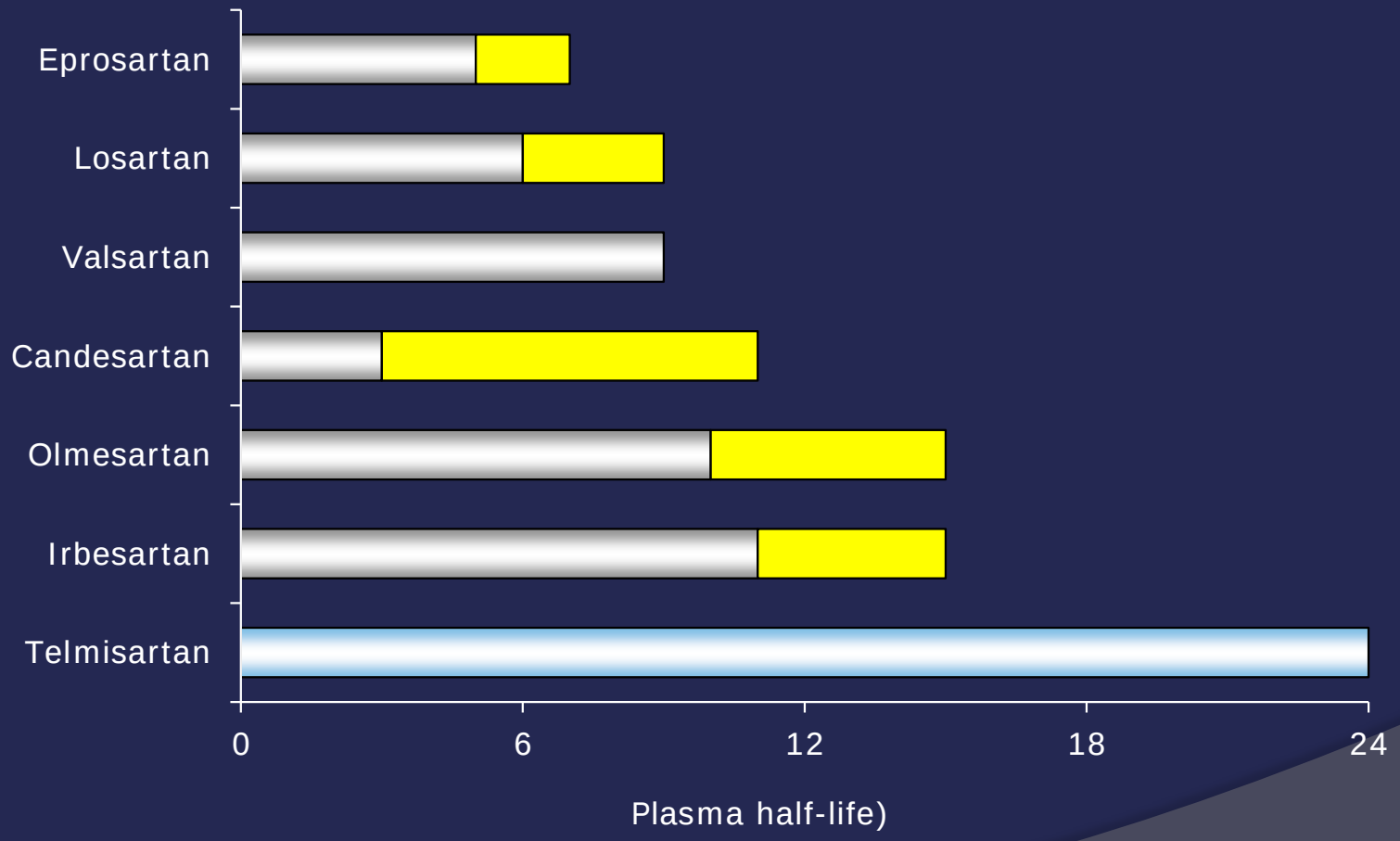
- No inhibition of ACE, bradykinin (no cough)

1B. ARB – „sartans“

ARBs are recommended for routine administration to symptomatic and asymptomatic patients with **an LVEF ≤ 40% who are intolerant to ACEI** for reasons other than hyperkalemia or renal insufficiency.

LVEF – left ventricular ejection fraction

1B. Angiotensin receptor blockers



1C. Renin Inhibitors

Aliskiren

MoA: orally active, direct action

reduce plasma renin activity by 50-70 %

D: once daily, 150 – 300 mg orally

I: monotherapy or combination with ACEI

2. Beta blockers

- Acts primarily by inhibiting the sympathetic nervous system.
- Competitive inhibition on β adrenoceptors
- Anti-arrhythmic properties.
- Anti-oxidant properties.

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)

Organ functions of B-B

- **cardiovascular system :** negative chronotropic and inotropic effect **=> ↓ of BP**
- **renal system: ↓ renin secretion**
- **bronchus: bronchokonstriction**
- **eye: ↓ of intraocular pressure**
- **Metabolic effects:** reduction of glykogenolysis and lipolysis

Classification of B-B

- **Non-selective (b1 + b2)** — **propranolol, metipranol**
- **(Cardio)selective (b1)** — **metoprolol, bisoprolol, betaxolol, atenolol**
- **Non-selective with ISA (b1 + b2)** — **pindolol**
- **(Cardio)selective (b1) with ISA** — **acebutolol, celiprolol**
- **Combining α + β blocade = β -blockers of II. generation** — **carvedilol, labetalol**

2. Beta – blockers practical issues

- Start at low dose and monitor for bradycardia
- Carvedilol, bisoprolol and metoprolol are the most commonly used for CHF amongst beta blockers

Carvedilol: 3.125 mg bid target: 25-50 mg bid
Metoprolol: 6.25 mg bid target: 75 mg bid
Bisoprolol: 1.25 mg qd target: 10mg qd

ADRs of BBs

- Fluid 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 pts with congestion
- decreasing the venous return
- have not proved effect on mortality

3. Diuretics

Loop diuretics **furosemide**

- the most effective – more intense and shorte diuresis
- commonly used in severe forms CHF
- combination with ACEI, spironolakton

Thiazides

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

Hydrochlorothiazid, indapamid

ADRs of diuretics

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

Potassium sparing diuretics

Spironolactone - Aldosterone antagonist

- Aldosterone inhibition minimize potassium loss, prevent sodium and water retention, endothelial dysfunction and myocardial fibrosis.

- Spironolactone can be added to loop diuretics to modestly enhance the diuresis; more importantly, improve survival.

4. Cardiac glycosides

- Come from foxgloves and related plants - containing several cardiac glycosides (digoxin is the most important therapeutically)…

Digitalis purpurea

Digitalis lanata

4. Cardiac glycosides - digoxin

Inhibition of Na+/K + ATPase pump increase intracellular sodium concentration → increase level of intracellular calcium ions

4. 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)

Pharmacokinetic of 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)

Practical issues with digoxin

- **How to give**

– General: 0.25 mg daily

– if > 70 yrs / renal insuff. / low lean body mass: 0.125 mg

- **Monitoring**

– Therapeutic range

– Toxicity common when > 2.0 ng/mL,
may occur at lower levels when↓K and ↓Mg

ADRs of digoxin

- Arrhythmias

–AV bloc

– Ectopic and re-entrant cardiac rhythms

- GI side effects

– Anorexia, nausea, vomiting

- Neurological complications

– Visual disturbance, disorientation, confusion

5. Other cardiac inotropes

Phosphodiesterase III Inhibitors
(Responsible for degradation of cAMP)

increase myocardial contractility

milrinone nad amrinone

5. Other cardiac inotropes

Sensitisation of cardiac muscle to calcium (also in vascular smooth muscle)

Levosimendan – Ca sensitizator

I: severe hearth failure

cardiogenic shock

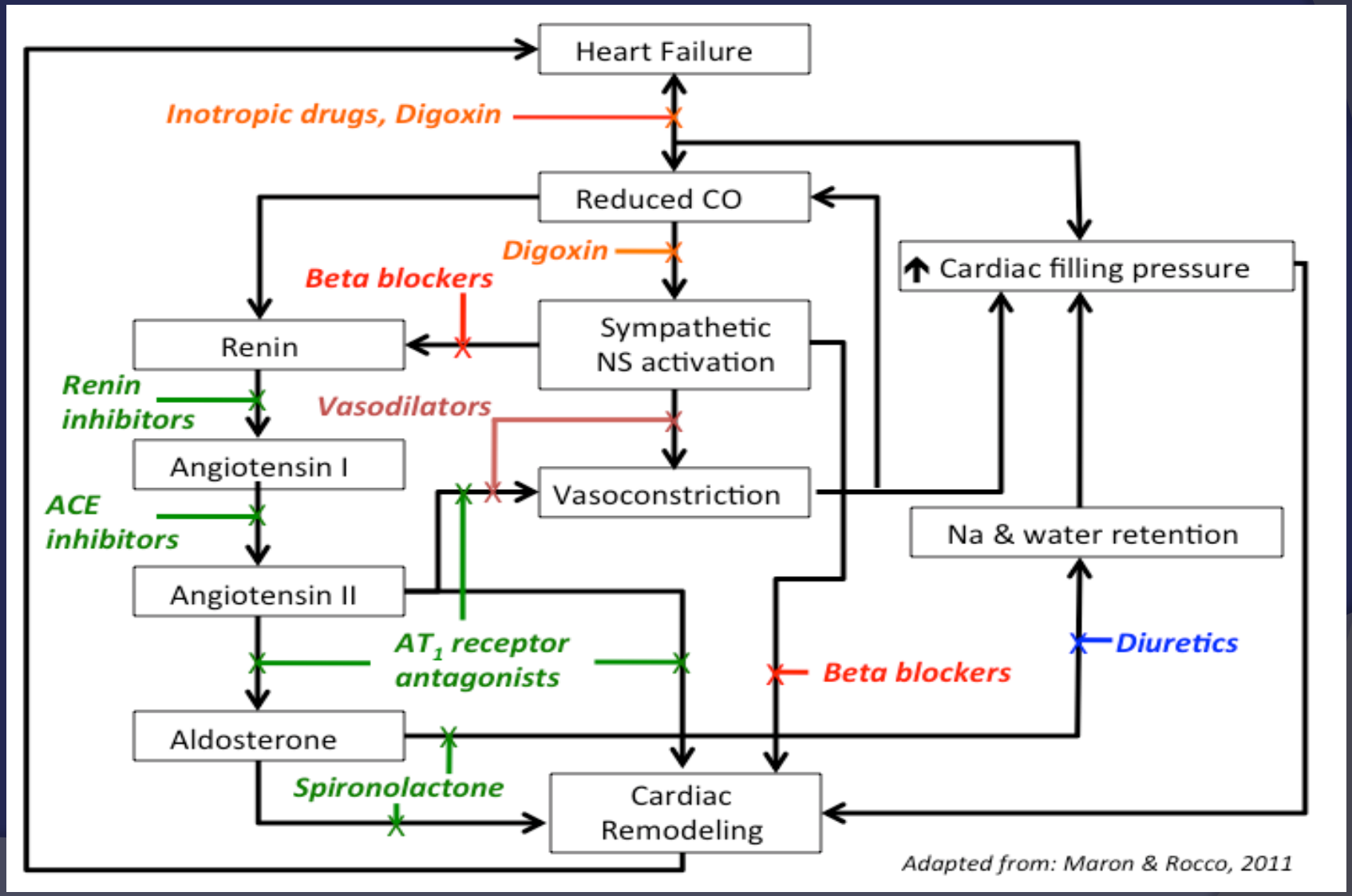
6. Other cardiac inotropes

Dobutamine is a beta-1 agonist which increase contractility and cardiac output.

Targets of CHF treatment

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

Sites of drug action in CHF therapy



DRUGS FOR CHF

Conclusion :

- ACE inhibitors are cornerstone in the treatment of CCF.
- Beta blockers are used in selected patients (mild/moderate failure, low dose)
- Diuretics and digoxin are other drugs useful in CCF in select patients.

ANTIARRHYTHMIC DRUGS

Mechanisms of Arrhythmogenesis

- **disorders of impulse generation** (abnormal automaticity, triggered activity
- **disorders of impulse conduction** (conduction block, reentry)
- **combination of both**

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

Most common arrhythmias in CHF

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

Atrial fibrillation

- Most common arrhythmia in HF
- Risk of trombo-embolic complication (stroke)
- **Therapy in REF (systolic HF)**
  1. B – blocker
  2. Digoxin (alternative or addition to BB)
  3. Amiodaron (alternative monotherapy or addition to BB or digoxin)
  4. AV node ablation and pacing
- **Therapy in PEF (diastolic HF)**
  1. Verapamil/ Diltiazem
- Trombembolism profylaxis

REF – reduced Ejection fraction, PEF – preserved ejection fraction

Amiodaron

- 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**
  - Hepatotoxicity
  - Arrhythmogenic effect
  - Alveolitis
  - Corneal deposits
  - Skin changes
  - Phototoxicity

Verapamil, diltiazem

- Non-dihydropyridine Ca^{++} channel blockers
- Reduction of heart rate
- Reduction of AV conduction
- **Contraindication** – concurrent use with B blockers, digoxin, atrioventricular blocks
- Common interactions - inhibition of CYP450

General principles for useof antiarrhythmic agents

- May predispose to ventricular arrhythmias
- Currently 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 (amiodaron, sotalol)