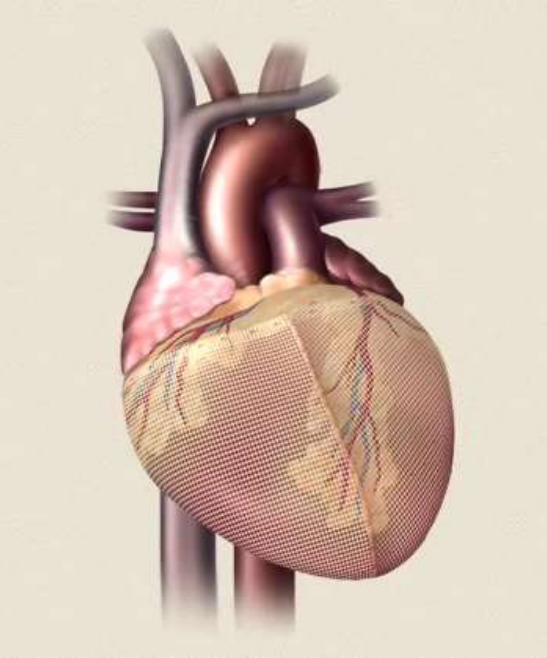
FARMAKOLOGI

OBAT DEKOMPENSATIO CORDIS

(Congesive Heart Failure/CHF)



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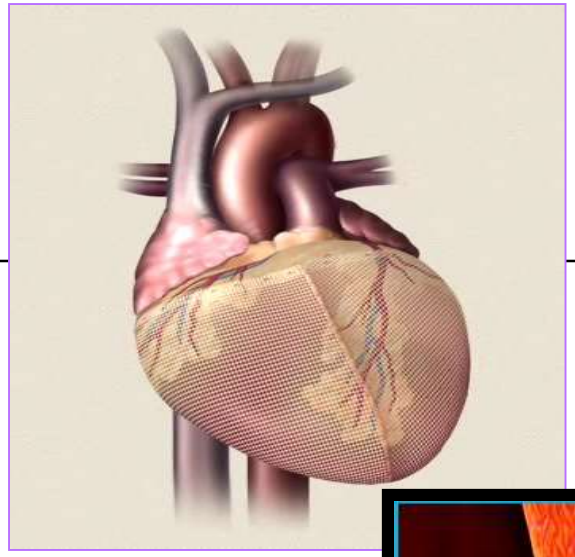
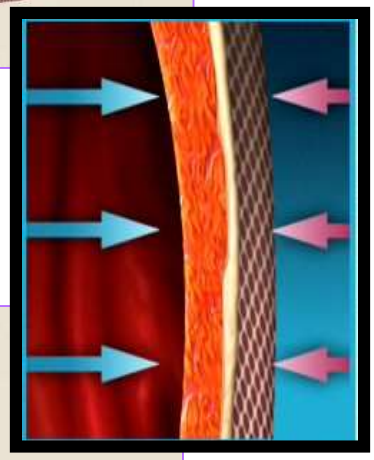
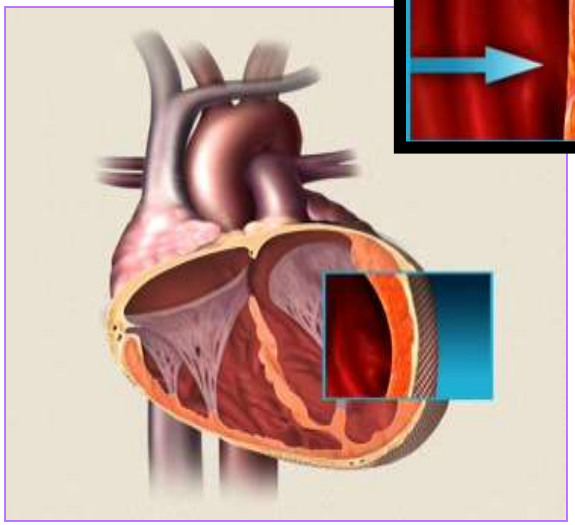
2021

- CHF = gangguan yg progresif
- Ciri khas= pembesaran jantung (Enlargement) disertai dg pe↓ kemampuan memompa darah.
- Enlargement → kompensasi jantung → fungsi mekanik & neurohumoral →progresif →ventricular remodeling







Performance ventrikel kiri ditentukan oleh :

- Preload
- Kontraktilitas miokard
- Afterload

Disfungsi :

- Disfungsi sistolik (*Heart Failure with Reduced Ejection Fraction*/HFrEF)
- Disfungsi diastolik (*Heart Failure with Preserved Ejection Fraction*/HFpEF)

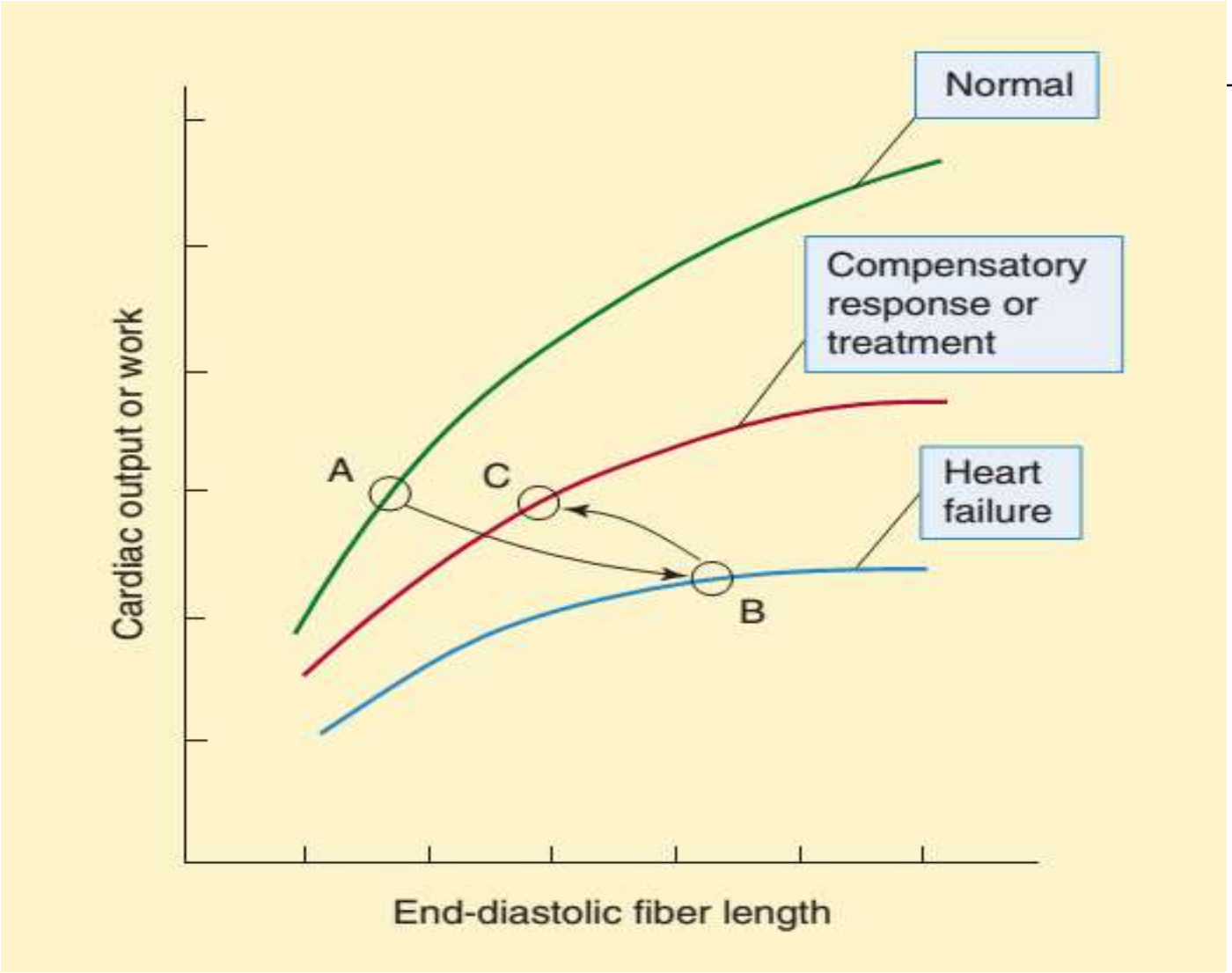
HFrEF

- dilatasi ventrikel dan kardiomegali
- berkurangnya kontraktilitas
- penurunan fraksi ejeksi yang signifikan (kurang dari 40%)

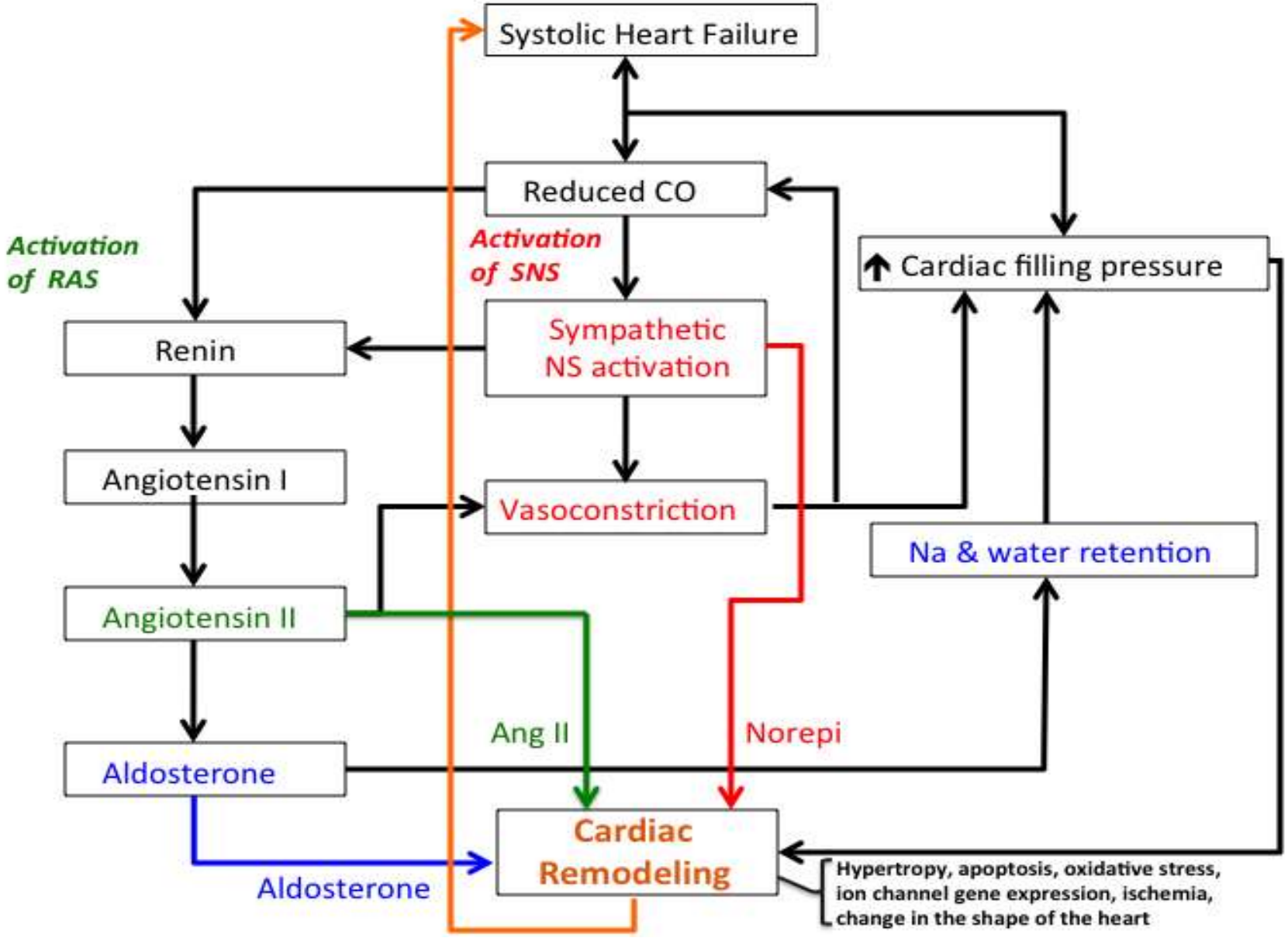
HFpEF

- penurunan kepatuhan ventrikel
- pengisian ventrikel selama diastole berkurang
- fraksi ejeksi yang relatif normal 50%, meskipun volume sekuncup berkurang secara signifikan

Kurva Fungsi ventrikel



Mekanisme Kompensasi utk mempertahankan MAP



The role of angiotensin II in the progression of heart failure

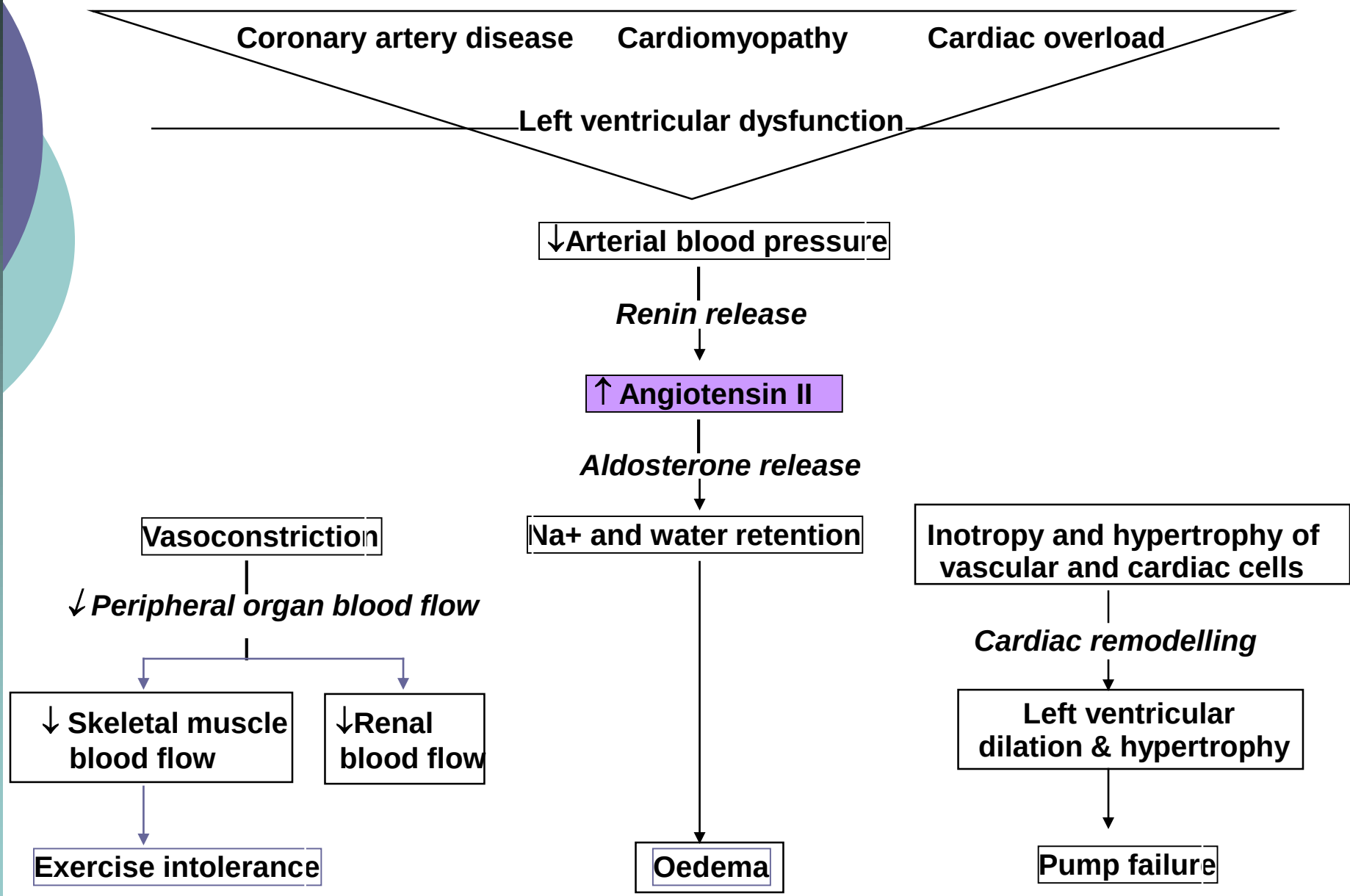
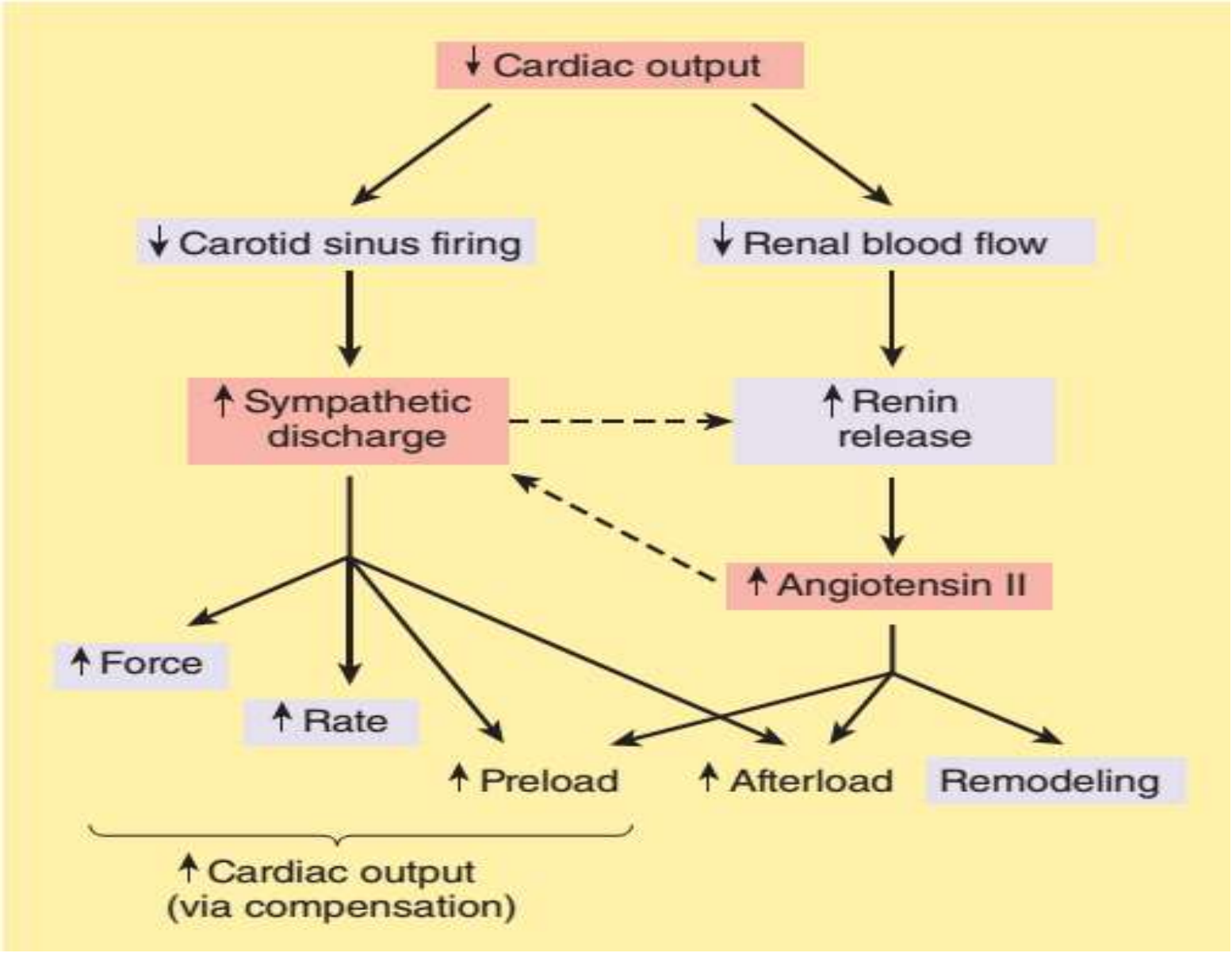


Table 33–2

Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

MECHANISM	PATHOPHYSIOLOGICAL EFFECT
Increased Na^+ and water retention	Edema, elevated cardiac filling pressures
K^+ and Mg^{2+} loss	Arrhythmogenesis and risk of sudden cardiac death
Reduced myocardial norepinephrine uptake	Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis
Reduced baroreceptor sensitivity	Reduced parasympathetic activity and risk of sudden cardiac death
Myocardial fibrosis, fibroblast proliferation	Remodeling and ventricular dysfunction
Alterations in Na^+ channel expression	Increased excitability and contractility of cardiac myocytes

Resume Kompensasi Neurohumoral



Klasifikasi CHF menurut NYHA

Kelas I : tidak ada simptom akibat aktivitas fisik (berjalan, naik tangga)

Kelas II : aktivitas fisik sedikit dibatasi karena dyspnea (naik tangga, jalan mendaki)

Kelas III : aktivitas fisik sangat dibatasi → dyspnea (dilarang berjalan jauh dan naik tangga)

Kelas IV : istirahat total → dyspnea saat istirahat (tidak dapat melakukan aktivitas fisik)

Klasifikasi CHF ,mnrt ACC/AHA 2001

- Stage A : Asymptomatic with no heart damage but have risk factors for heart failure
- Stage B : Asymptomatic but have signs of structural heart damage
- Stage C : Have symptoms and heart damage
- Stage D : Endstage disease

Tujuan Terapi CHF

- Memperbaiki symptoms & kualitas hidup
  →Tx simptomatik (Diuretik)
  → Me↑ fungsi jantung (Inotropik positif, Vasodilator)

- Me ↓ progressifitas CHF→Menghambat adaptasi neurohormonal yg merugikan (Beta bloker, Antagonis Angiotensin (ACEi &AIIRA), Antagonis Aldosteron)

- Me ↓ resiko kematian & kebutuhan rawat inap

Farmakotx Disfungsi Sistolik (HFrEF)

Initial Tx :

- ***ACE Inhibitors***: captopril, enalapril, ramipril
- ***ARBs***: losartan, valsartan
- ***Beta blockers***: metoprolol, carvedilol
- ***Neprilysin Inhibitor / ARB Combination***: sacubitril + valsartan

Secondary Therapy :

- ***Aldosterone Antagonists***: spironolactone
- ***Vasodilators***: nitrates (nitroglycerin, isosorbide dinitrate),nitroprusside, hydralazine, nesiritide
- ***Positive inotropes***: digoxin, dobutamine, dopamine

Farmakotx Disfungsi Diastolik (HFpEF)

- Management of associated conditions:
  - Hypertension
  - Myocardial Ischemia
  - Hyperlipidemia
  - Atrial Fibrillation
  - Edema

Farmakotx Edema &Reverse Cardiac Remodelling

Treatment of Peripheral Edema :

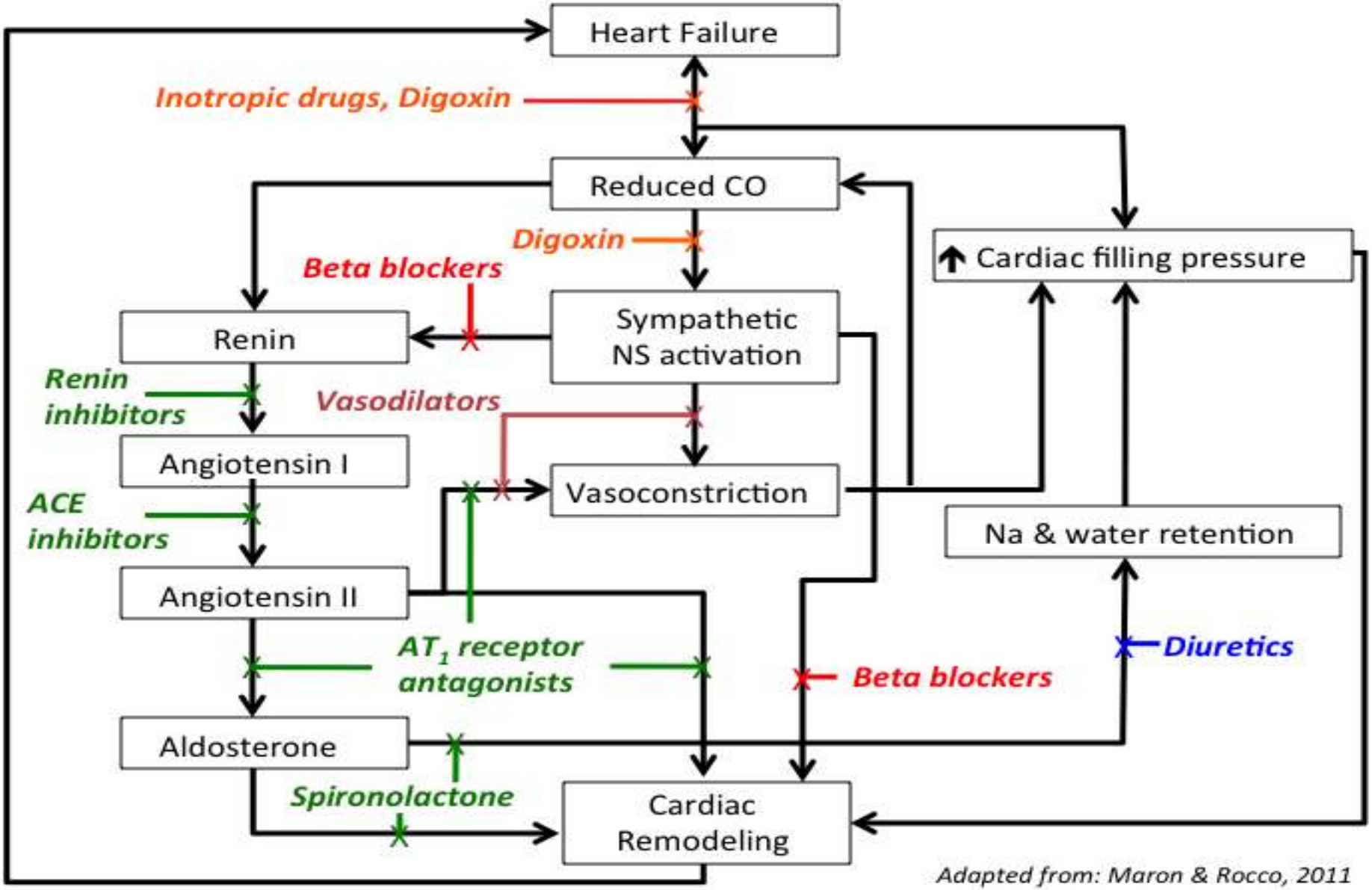
- ***Diuretics*:** dapagliflozin, loop diuretics (furosemide, torsemide), chlorthalidone

Treatment of Pulmonary Edema

- Morphine
- Furosemide
- Nitroglycerin
- Supplemental Oxygen

Reverse Cardiac Remodelling

- ACEi
- ARB
- Beta blocker
- Aldoseteron Antagonis
- Neprilysin inhibitor


Heart Failure
Inotropic drugs, Digoxin
Reduced CO
Digoxin
Beta blockers
Cardiac filling pressure
Renin
Sympathetic NS activation
Renin inhibitors
Vasodilators
Angiotensin I
Vasoconstriction
ACE inhibitors
Na & water retention
Angiotensin II
AT1 receptor antagonists
Diuretics
Beta blockers
Aldosterone
Spironolactone
Cardiac Remodeling
Adapted from: Maron & Rocco, 2011

Faktor yg Memperberat CHF

- iskemia / infark miokard
- Diet mengandung Na berlebihan
- Intake cairan berlebihan
- Tidak patuh dalam berobat
- Arritmia
- Kondisi yg berhub dg pe ↑ metabolisme (kehamilan, tirotoksikosis, aktivitas fisik berlebihan)
- Pemakaian obat yang bersifat inotropik negatif atau retensi cairan (mis. NSAID, kortikosteroid)
- Alkohol

Perbaikan Performance Jantung

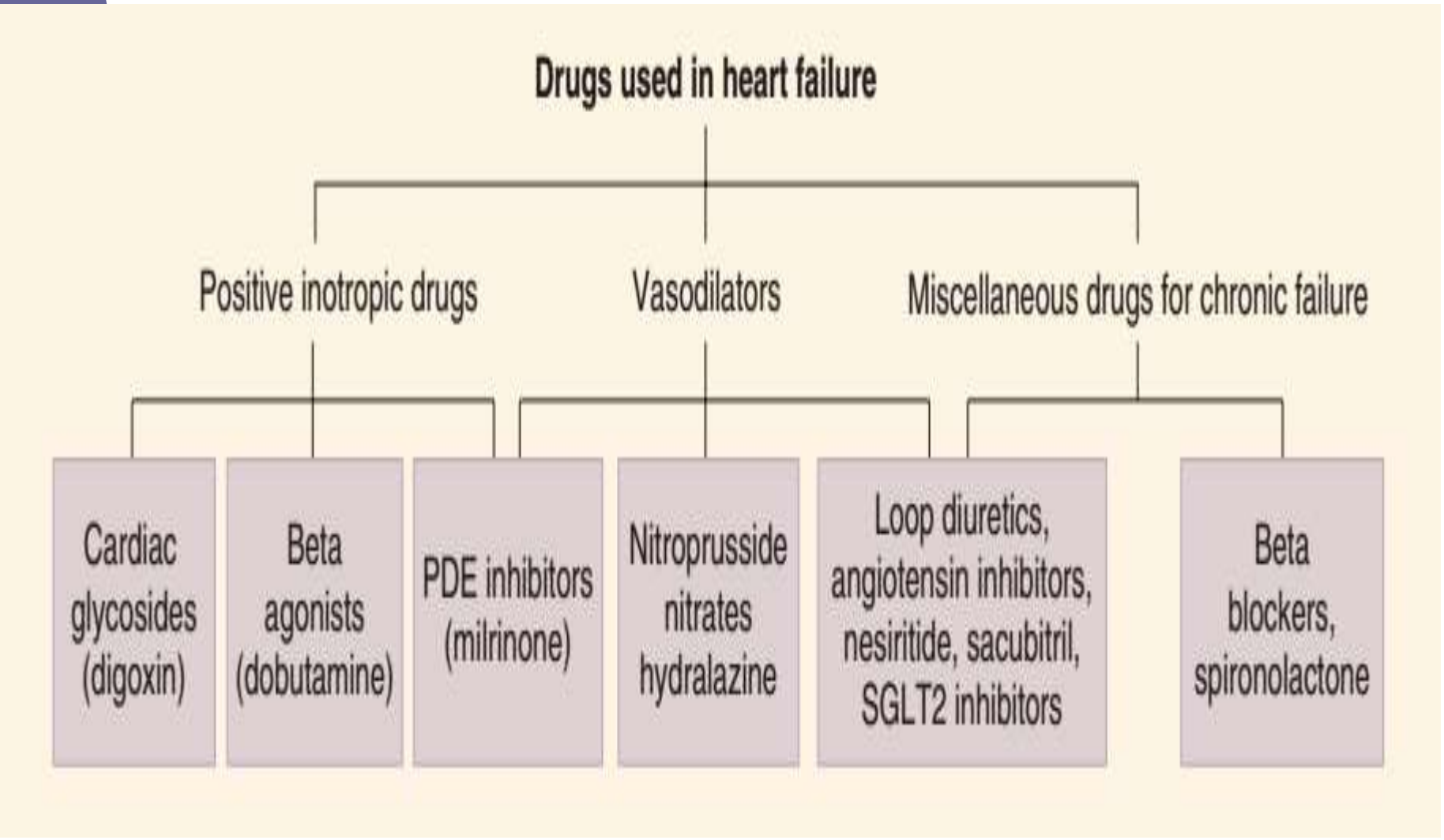
Preload: (**Atrial Pressure**) Increased in heart failure due to increased blood volume and venous tone Treated with salt restriction and diuretics

Afterload: (**Vascular Resistance**) Increased due to reflex sympathetic outflow and renin-angiotensin system though elevated **afterload** may further reduce cardiac output Reduction of arterial tone

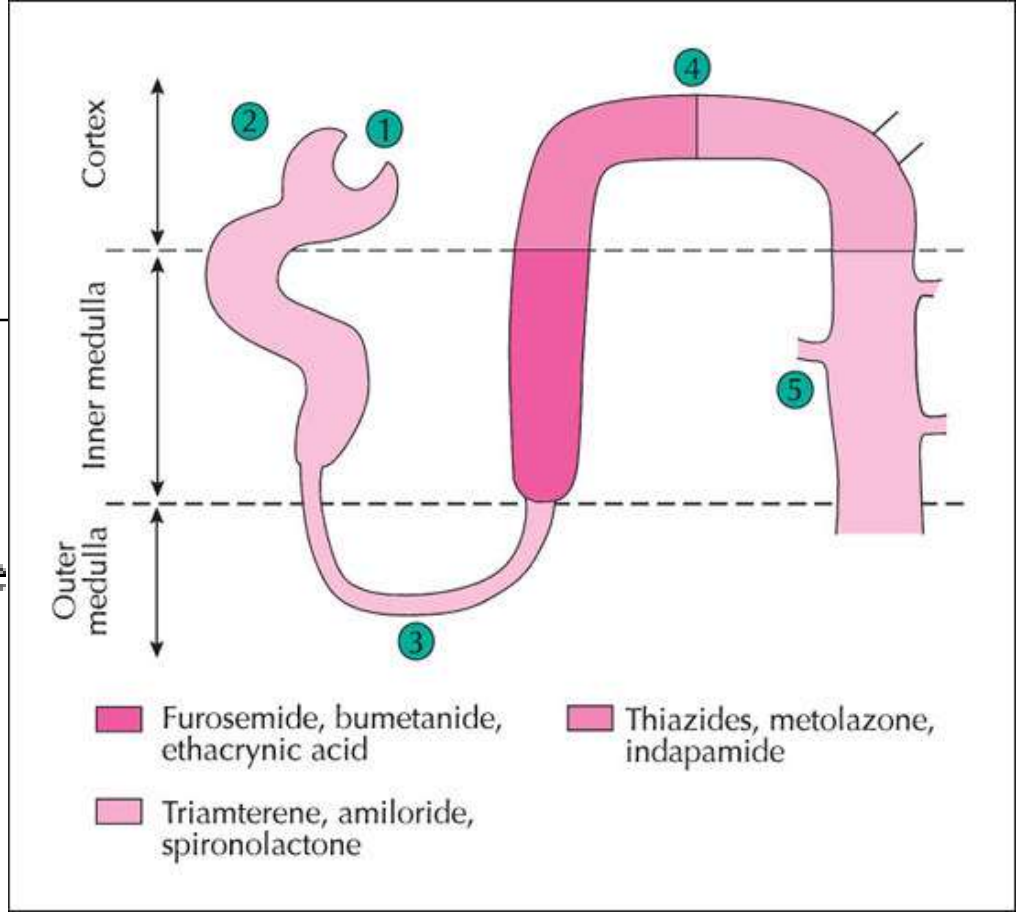
Contractility: Reduction in intrinsic contractility and therefore reduction in pump performance Inotropic drugs to increase contractility

Heart Rate: Increases through sympathetic NS compensation

Target or Drug Class	Drug Examples	Mechanisms	Uses in Heart Failure
Na^+/K^+ ATPase inhibitors	Digoxin	Increases Ca_i, increases cardiac contractility	Chronic failure
Renal sodium transporter inhibitors	Furosemide, spironolactone, other diuretics; SGLT2 blockers	Reduce preload and afterload	Acute and chronic failure
ACE inhibitors, Angiotensin receptor blockers	Captopril, others Losartan, others	Reduce preload and afterload, reduce remodeling, other	Chronic failure
Beta adrenoceptor antagonists	Carvedilol, others	Reduce afterload, reduce remodeling, other	Chronic stable failure
Beta adrenoceptor agonists	Dobutamine, dopamine	Increase Ca_i, increase contractility	Acute failure
Vasodilators	Nitroprusside	Reduce preload and afterload	Acute failure
Phosphodiesterase inhibitors	Milrinone	Vasodilation, increase contractility	Acute failure
Natriuretic peptide	Nesiritide	Vasodilation reduces preload and afterload; some diuretic effect	Acute failure
Neprilysin inhibitor + ARB	Sacubitril/Valsartan	Combined increased BNP + ARB effects	Chronic failure


Drugs used in heart failure
Positive inotropic drugs
Vasodilators
Miscellaneous drugs for chronic failure
Cardiac glycosides (digoxin)
Beta agonists (dobutamine)
PDE inhibitors (milrinone)
Nitroprusside nitrates hydralazine
Loop diuretics, angiotensin inhibitors, nesiritide, sacubitril, SGLT2 inhibitors
Beta blockers, spironolactone

DIURETIK



- Drugs: Diuretics (e.g. Furosemide
- Mechanism: Lower blood volume
- Indications: Useful in almost all Heart Failure patients
  - Loop diuretics — Furosemide, acute pulmonary edema & severe, chronic heart failure
  - Thiazides — Hydrochorothiazide, Mild chronic failure
  - Spironolactone — Aldosterone antagonist
- Side-effects: Hypokalemia

DIURETIK

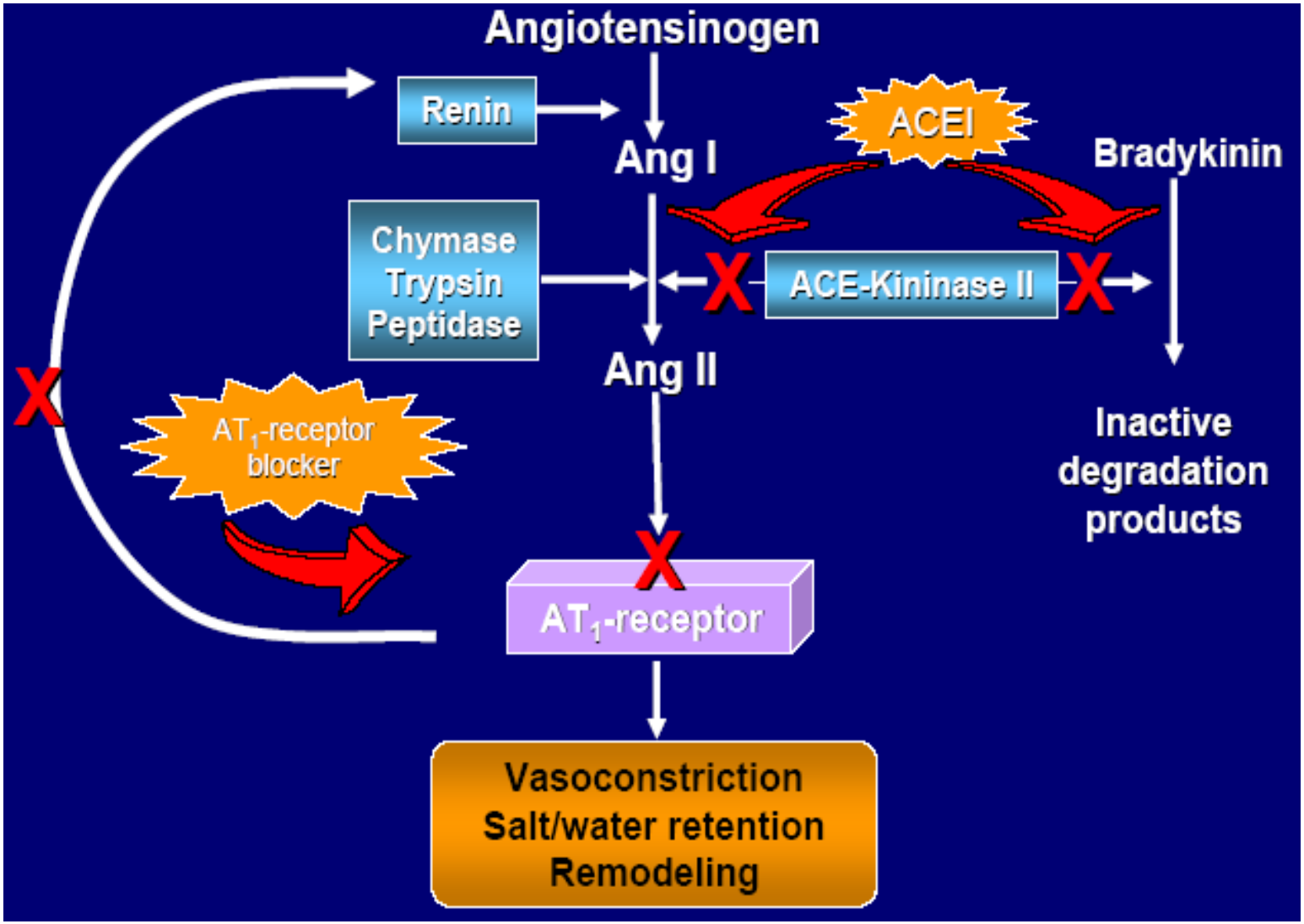
HYDROCHLORTHIAZIDE (HCT)

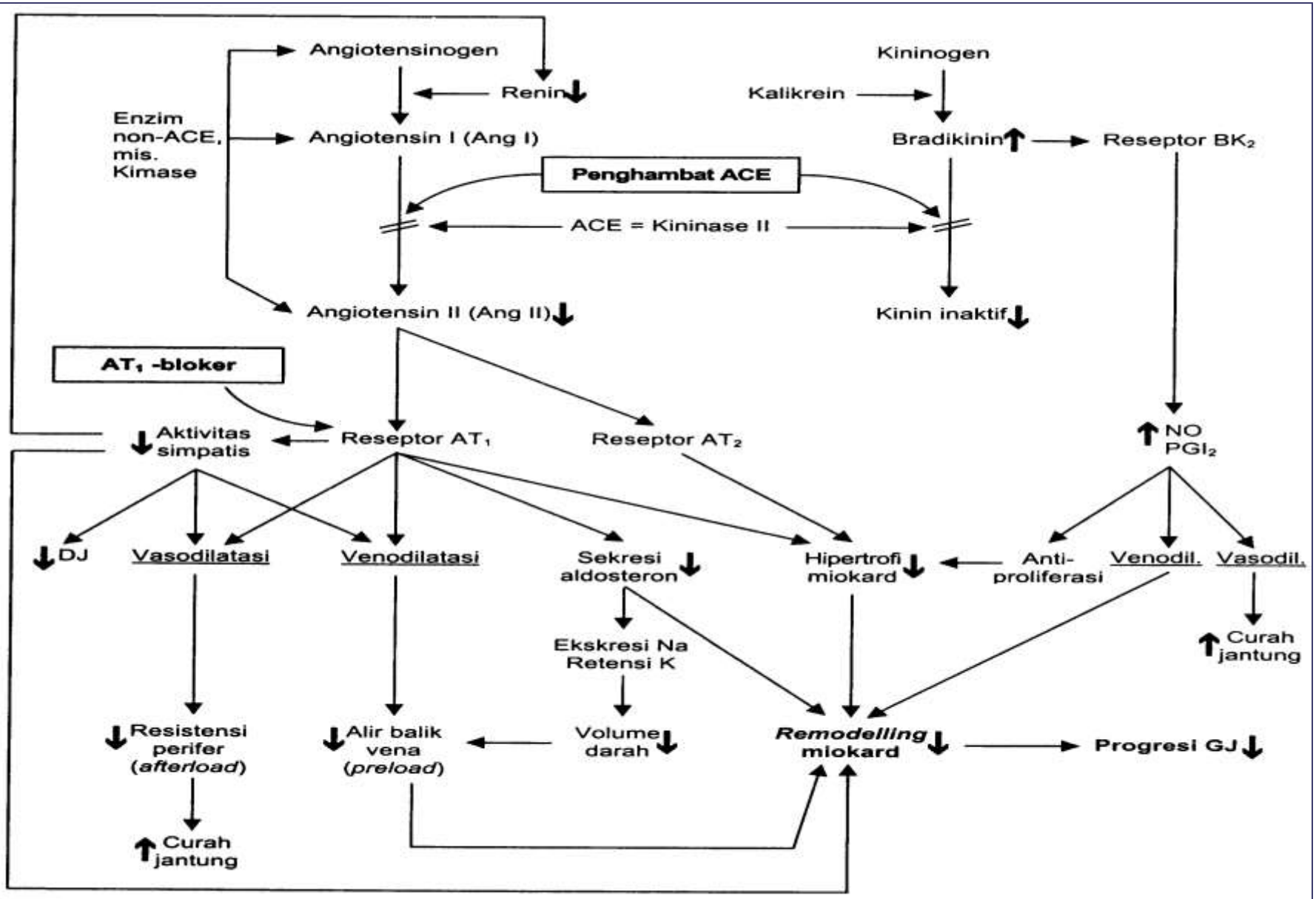
- Prototipe Thiazide
- Efek : diuretic, vasodilatasi
- Formulasi pasien CHF, serring dikombinasi :
  - aliskiren + amlodipine + HCT
  - amlodipine + HCT
  - candesartan + HCT
  - losartan + HCT
  - methyldopa + HCT
  - quinapril + HCT

FUROSEMID

- Efek : diuretic >>, vasodilatasi < (dp thiazide)
- DOC utk pasien CHF dg edema berat, acute lung edema
- KI= pasien alergi sulfa

ANGIOTENSIN ANTAGONIST





Gambar 19-2. Mekanisme kerja penghambat ACE dan antagonis AII dalam terapi gagal jantung
(PG = prostaglandin; ACE = *angiotensin converting enzyme*; DJ = denyut jantung; GJ = gagal jantung; AT_1 = reseptor angiotensin tipe 1; AT_2 = reseptor angiotensin tipe 2)

ANGIOTENSIN ANTAGONIS

- Drugs: ACE inhibitors (e.g. Captopril) & Receptor Antagonists (e.g. Losartan)
- Mechanism: Reduce Angiotensin II synthesis ACE inhibitors
  Block AT1-type receptors Angiotensin receptor inhbitors
- Indications: First line agents (with diuretics) in Heart Failure
  AT1-type antagonists used if ACE inhibitors are not tolerated
- Side-effects: Renal Damage ACE inhibitors
  Contraindicated in Pregnancy AT1 antagonists

ACEI

- Reduce angiotensin II and aldosterone levels &
- reduce sympathetic nervous system activity
- more potent arterial than venous dilators.
- Left ventricular filling pressure and volume are reduced in association with decreased total peripheral resistance.
- reduce the development of cardiac remodeling

- β-Blockers: **Metoprolol**, prolong life in chronic heart failure

  Mechanism unknown may involve reduced renin secretion

- β-Agonists: **Dobutamide**, β1 selective for severe heart failure

  Increases cardiac force, reduces afterload result of increasing cardiac output

- Phosphodiesterase Inhibitors: **Theophylline**, acute decompensation in HF

  Increases cAMP levels in cardiac and vascular tissue

- Vasodilators: **Nitroglycerin**, acute decompensation in Heart Failure

  Reduce afterload (increasing ejection fraction) and preload (reduce myocardial O_2 requirement)

INOTROPIK POSITIF

DOBUTAMIN

- β1 selective adrenergic agonist
- Indikasi :
  - Terapi jangka pendek pasien CHF yang mengalami penurunan kontraktilitas
- ES : peningkatan sistolik :10-20mmHG, HR :5-15x/mnt

DOPAMIN

- Sympatomimetik, precursor NE
- **Pd dosis rendah (1-2ug/kg/min) → agonis selektif R/*D1*** pd bbrp p.d → vasodilatasi
- **Aktivasi R/D1 renal → Tx shock**
- Aktivasi presynaptic R/D2 → suppress NE release.
- **Pd dosis intermediate (5-10 ug/kg/ min)**→ aktivasi R/*β1* di jantung
- Pd dosis tinggi (>10 ug/kg/min)→ aktivasi R/*α* → vasokonstriksi
- **Indikasi** = perbaikan hemodinamik pd syok akibat IMA, trauma, sepsis endotoksik, gagal ginjal, gagal jantung

INOTROPIK POSITIF

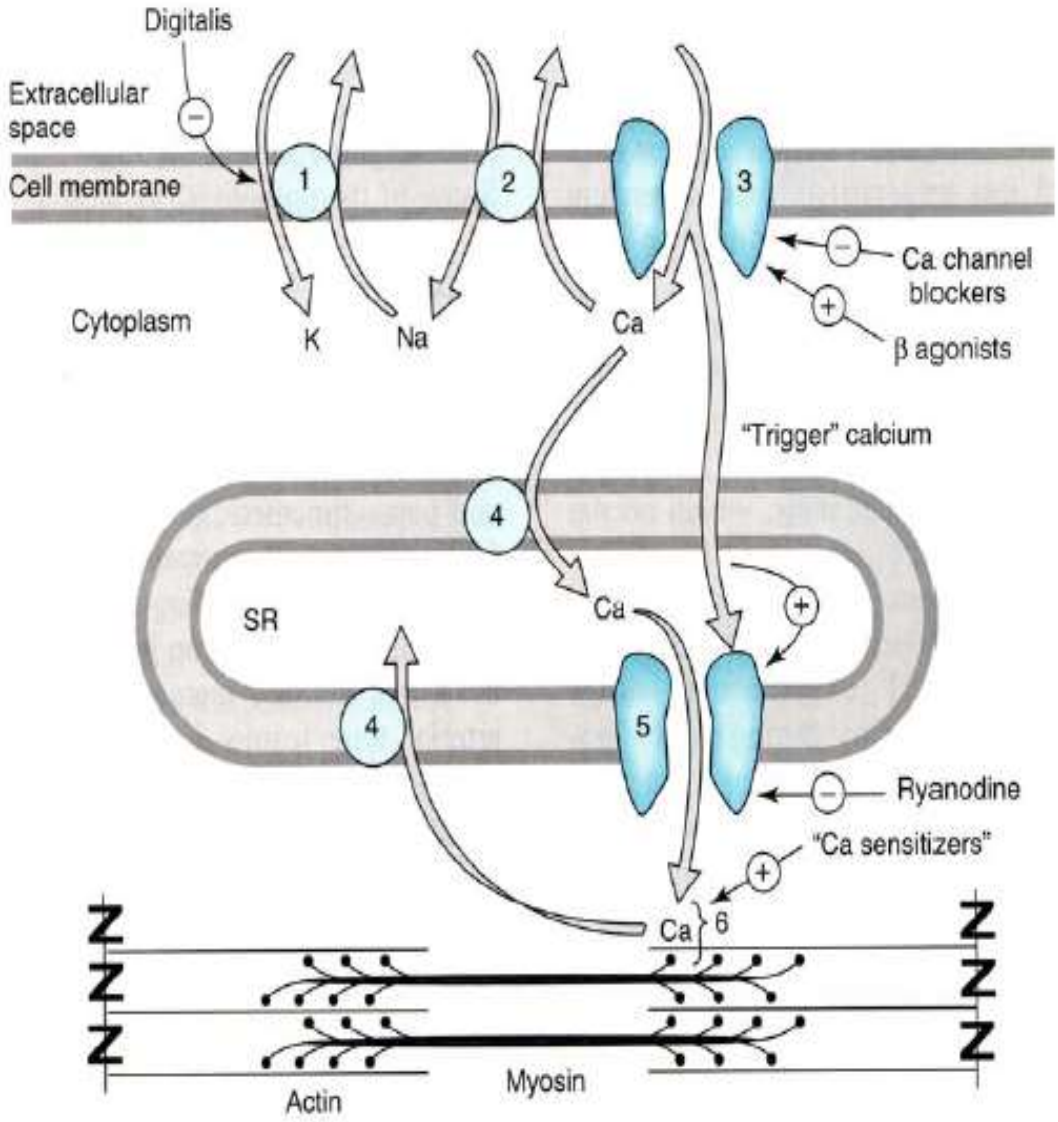
DOPAMIN

- ES= arritmia, dyspnea, headache
- Interaksi =
  - dg obat simpatomimetik yg lain → potensiasi
  - dg simpatolitik→ melemahkan efek

DIGOKSIN

- Hamb Na/K ATPase
- Mempunyai efek sistemik pd baroreseptor & sist parasimpatis →me↑tonus vagal→control ventricular rate u/ pasien atrial takiaritmia
- Indikasi :HFrEF yg msh ada symptom stl tx diuretic dan ACEi

DIGOKSIN



Digoxin block of Na^+/K^+ ATPase

↓

Less expulsion of cytosolic Ca^{2+} by Na^+/Ca^{2+} exchanger

↓

Increased elevation cytosolic Ca^{2+} from sarcoplasmic reticulum

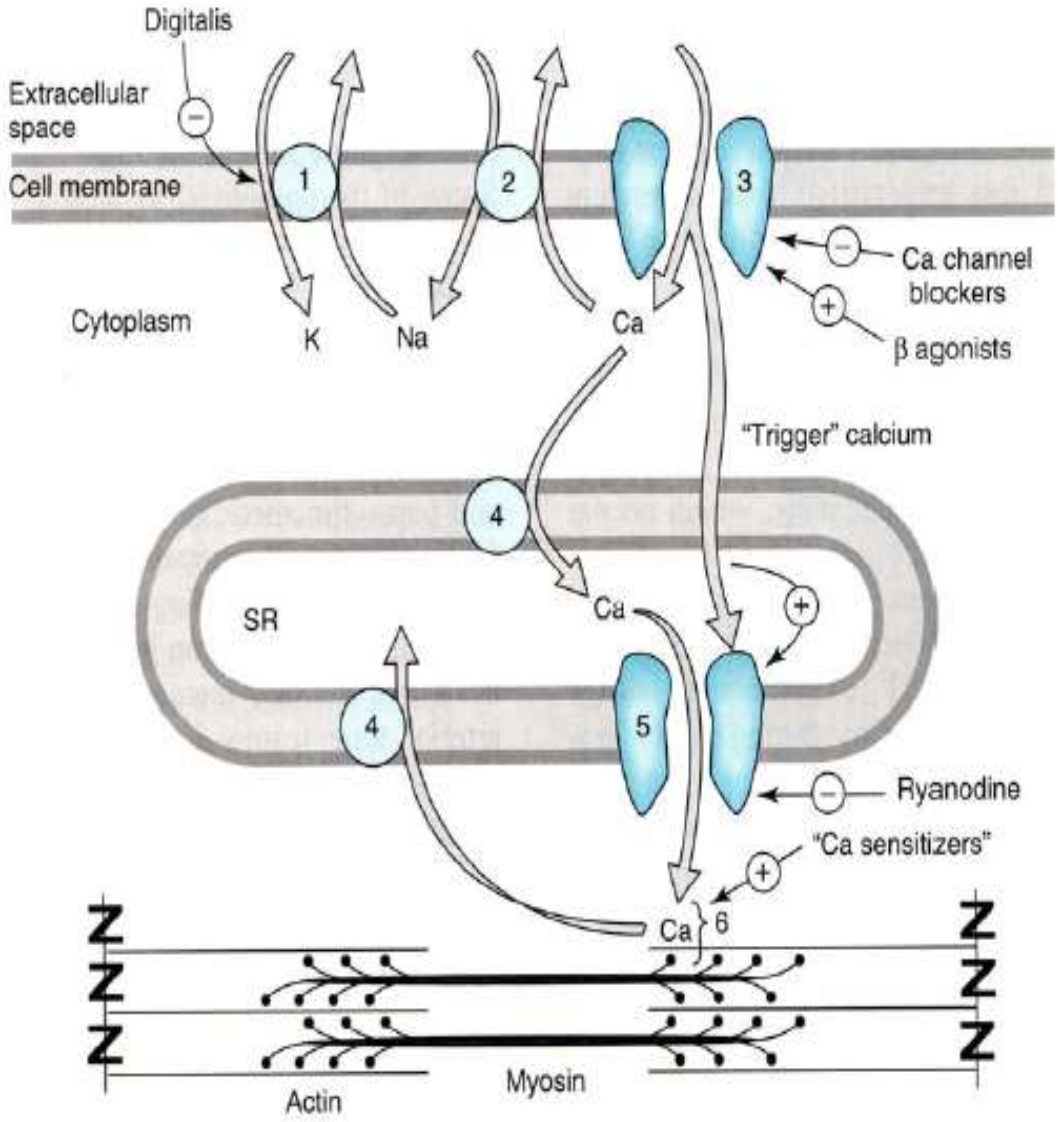
↓

Increased Contractility

DIGOKSIN

- increase in the force of contraction → benefit in patients with systolic heart failure
- used in patients with moderate to severe heart failure as a secondary or tertiary tx
- reduce/control the ventricular rate by increasing vagal tone to the AV node → benefit for patient with atrial fibrillation

DIGOKSIN



Digoxin block of Na^+/K^+ ATPase

↓

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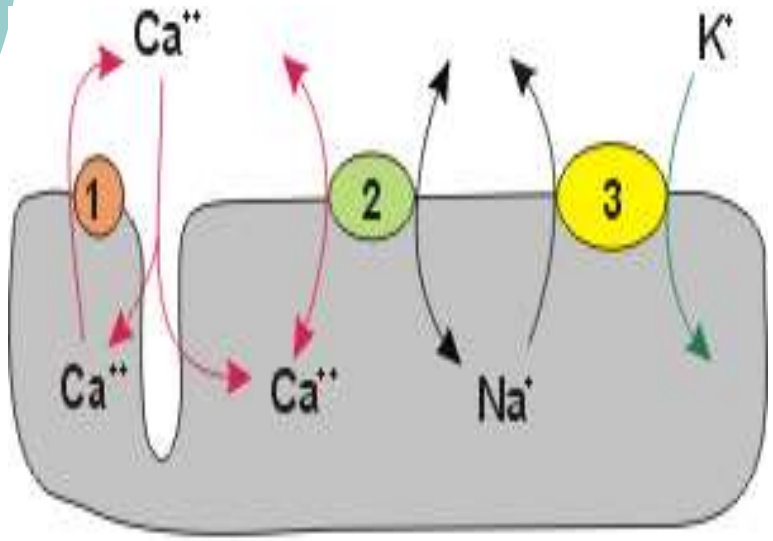
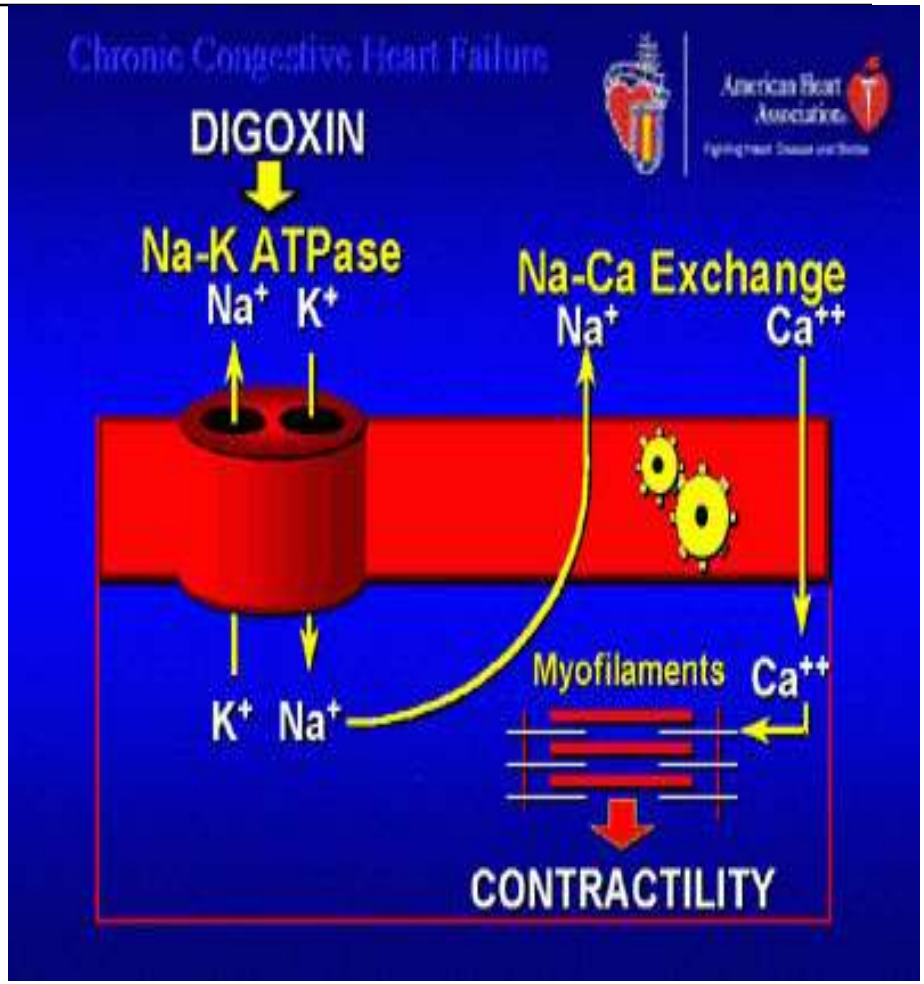
Increased elevation cytosolic Ca^{2+} from sarcoplasmic reticulum

↓

Increased Contractility



1 = ATP-dependent Ca^{++} pump
2 = Na^{+}/Ca^{++} exchanger
3 = Na^{+}/K^{+}-ATPase pump



Intoksikasi Digitalis

INTERAKSI OBAT :

K- depleting diuretic (hipokalemi meningkatkan efek/toksisitas digoksin brp aritmia). Hipokalemia menginduksi pe↓ aktivitas Na/K ATPase (diregulasi o/ kdr K ekstrasel)
Amiodaron, verapamil, itrakonazole, quinidine (menurunkan ekskresi renal)
eritromisin, klaritromisin, tetrasiklin (flora normal mati, hamb first pass di usus, meningkt bioavaibilitas)

Intoksikasi Digitalis

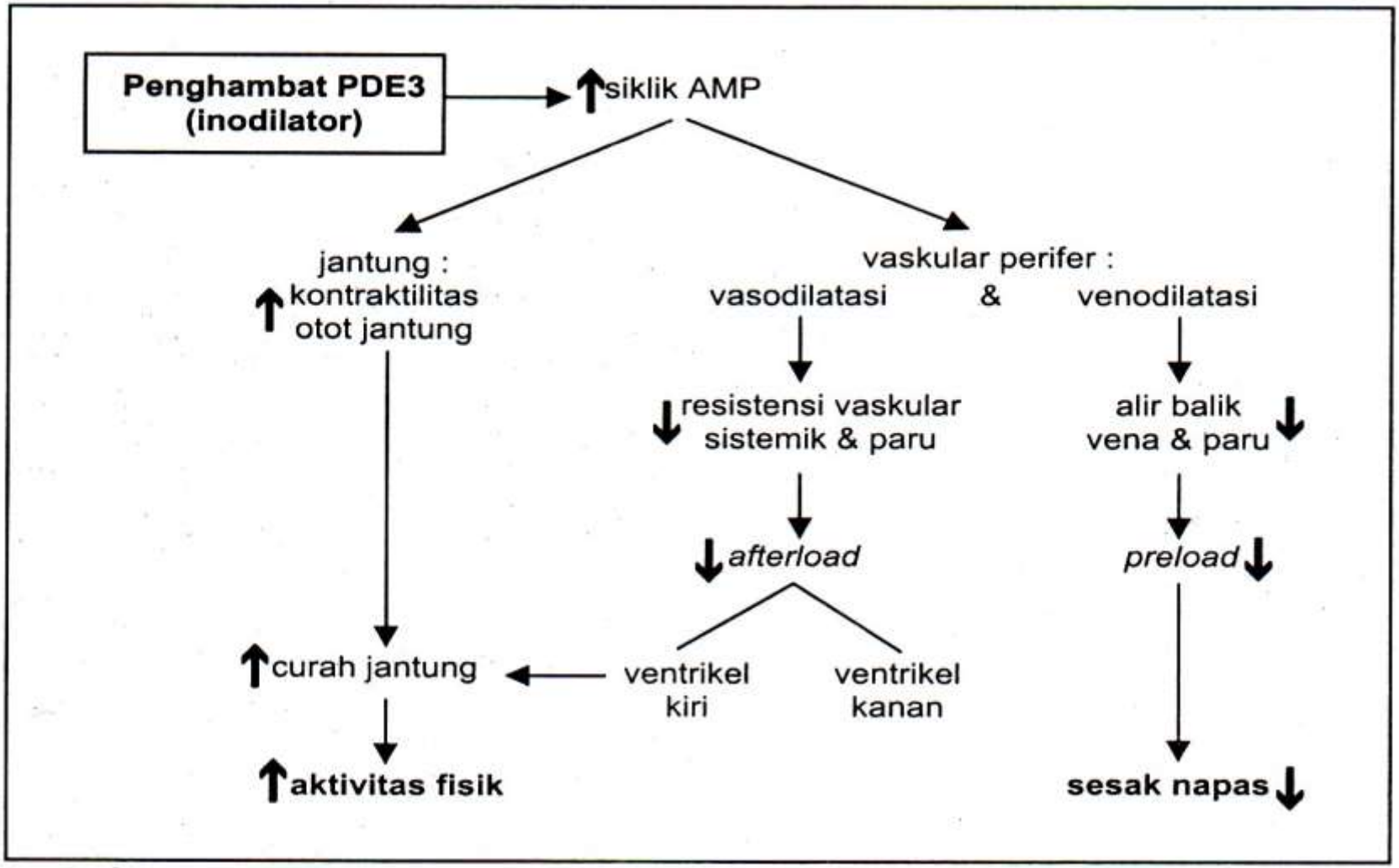
GEJALA EKSTRA CARDIAC:

- Gastrointestinal : mual muntah nausea anoreksia
- Neuromuskular : kelemahan otot, fatigue
- Psikis : cemas, halusinasi, delirium
- keluhan mata : kabur, foto pobi pandangan kuning

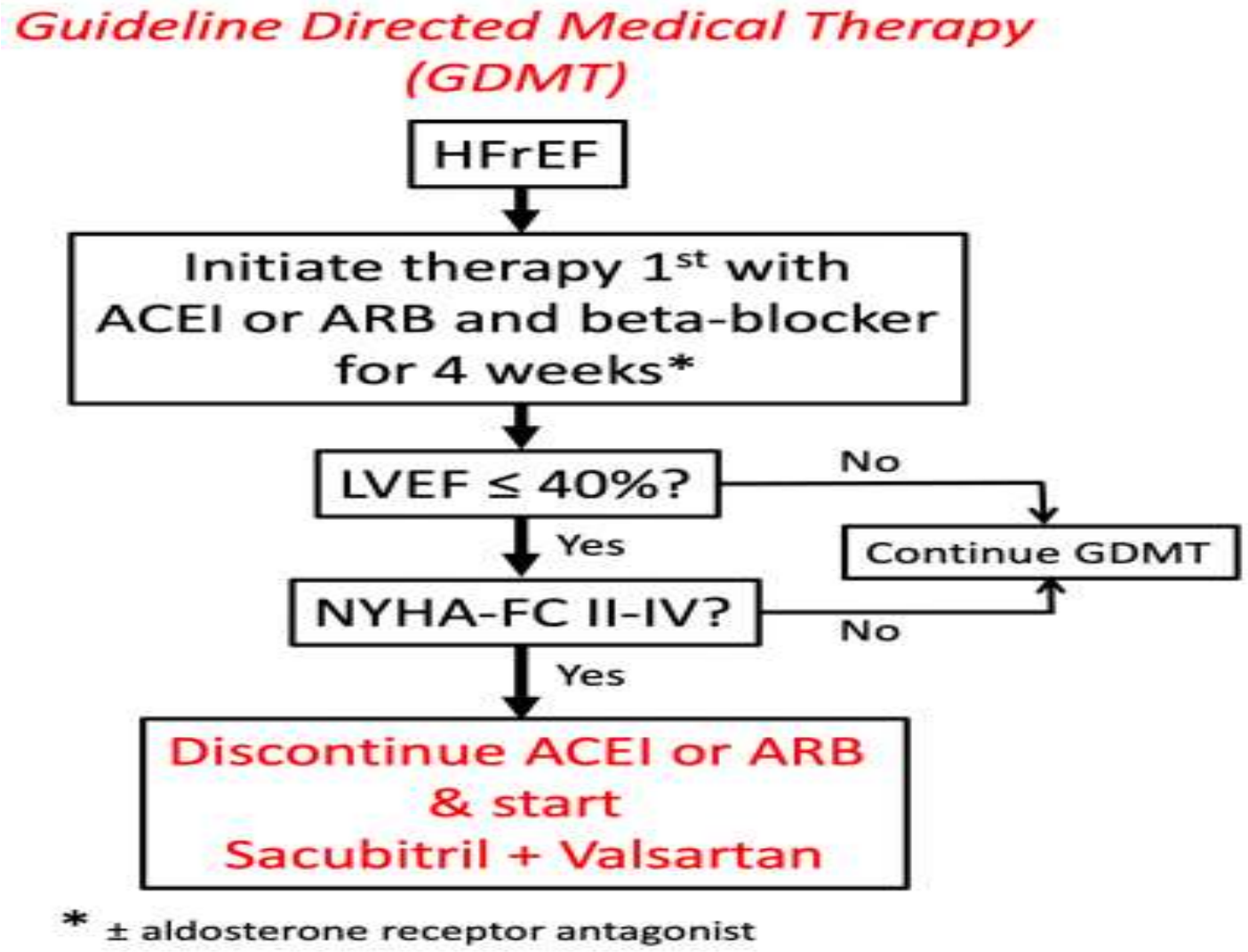
GEJALA INTRA CARDIAC :

- bradikardi
- perlambatan konduksi a-v→AV blok drjt 2-3 (tx dg atropine)
- ventrikular takhi kardi
- ventrikular fibrilasi

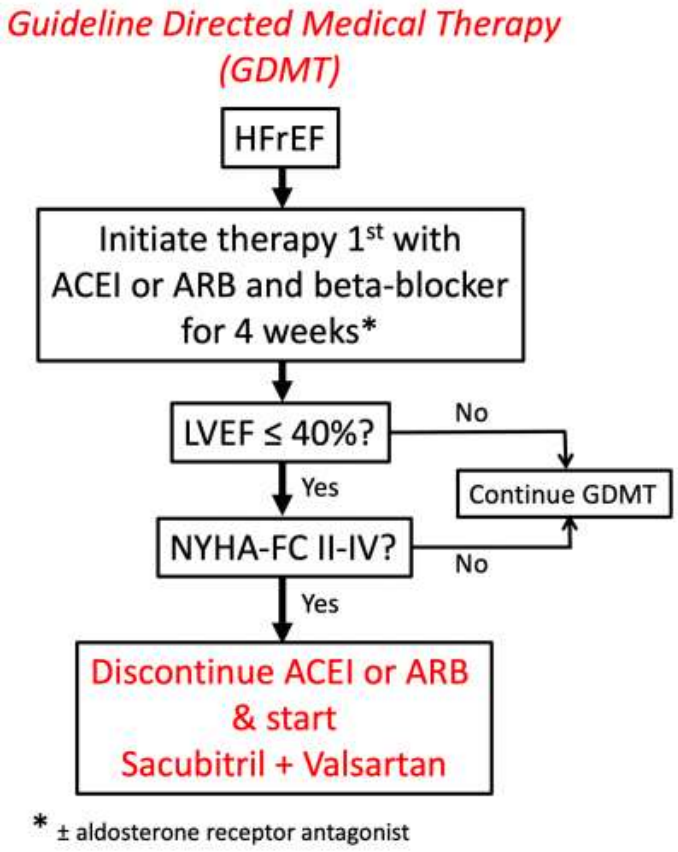
PDE INHIBITOR (TEOFILIN)

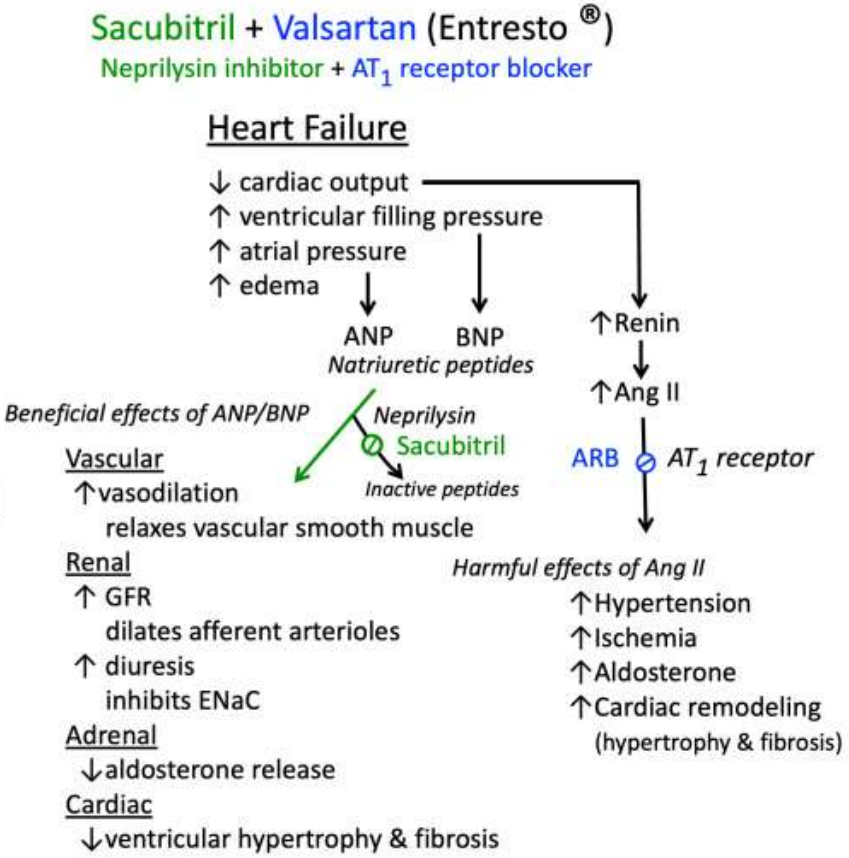


GUIDELINE TX HFrEF



ANGIOTENSIN RECEPTOR – NEPRILYSIN INHIBITOR (ARNI)
= komb Sacubitril/ valsartan





Beta Bloker

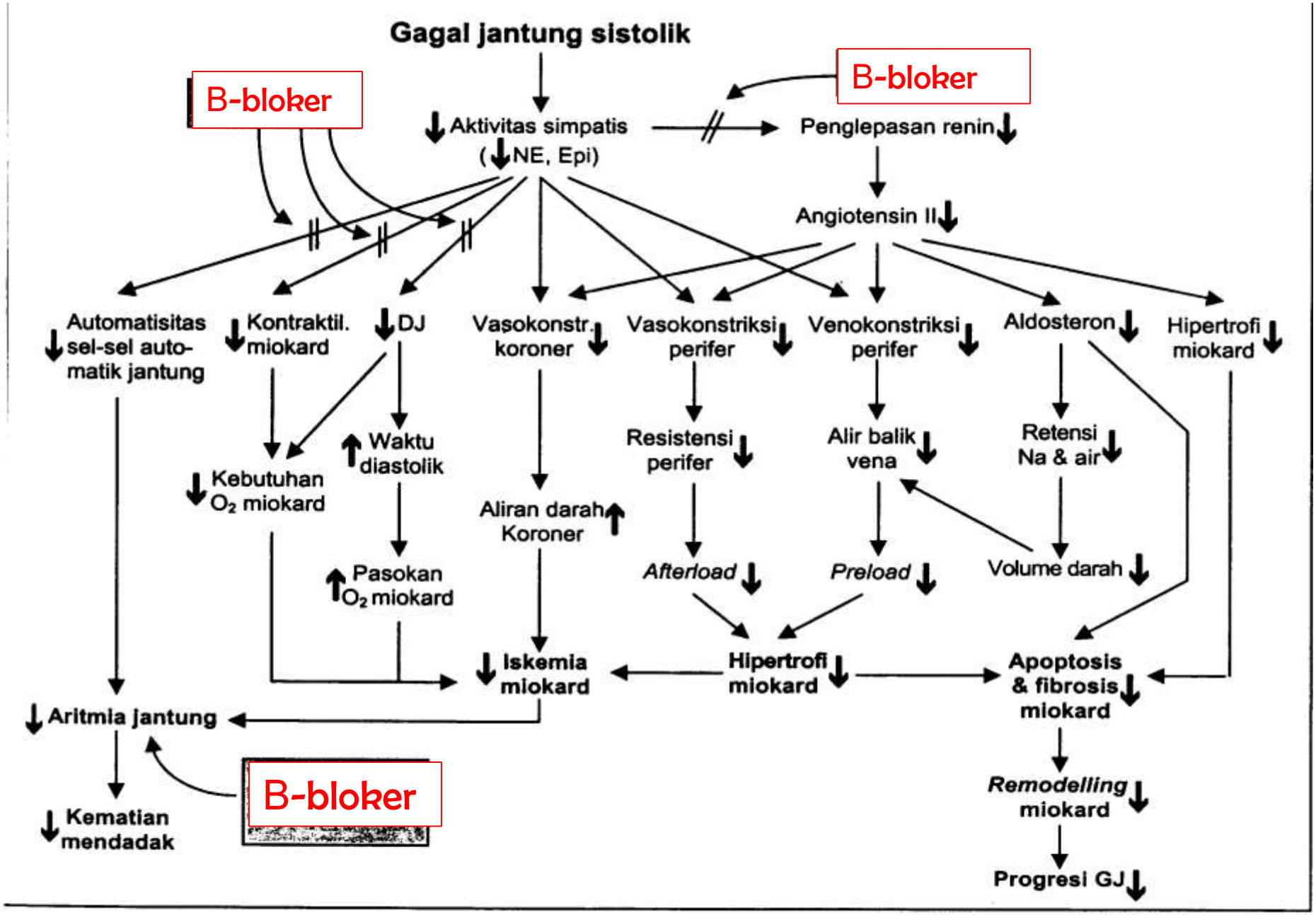
Metoprolol : β-1 selective
Carvedilol : mixed α-1 and non-selective β receptor antagonist.

HF sistolik

- pe↓cardiac remodeling akibat pe↑katekolamin dan takikardi kronik

HF diastolik

- Relaksasi miokard →memfasilitasi diastolic filling
- Bersama ACEi/ARB menghamb aktivasi neurohumoral (RAAS)



Gambar 19-3. Mekanisme kerja β-bloker pada gagal jantung sistolik
(NE = norepinefrin; Epi = epinefrin; GJ = gagal jantung)

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Diuretics				
Furosemide, other loop diuretics	Reduces preload, edema by powerful diuretic action on thick ascending limb in nephron • vasodilating effect on pulmonary vessels	Acute and chronic heart failure, especially acute pulmonary edema • other edematous conditions, hypercalcemia (see Chapter 15)	Oral, parenteral Duration: 2–4 h	Ototoxicity • hypovolemia, hypokalemia
Spironolactone	Antagonist of aldosterone in kidney plus poorly understood reduction in mortality	Chronic heart failure, aldosteronism	Oral Duration: 24–48 h	Hyperkalemia • gynecomastia
Eplerenone: similar to spironolactone but lacks gynecomastia effect *Flozins: empagliflozin, dapagliflozin, canagliflozin:* SGLT2 inhibitors used to reduce the risk of cardiovascular death in type 2 diabetics				
Angiotensin-converting enzyme (ACE) inhibitors and receptor blockers				
Captopril	Blocks angiotensin-converting enzyme, reduces Ang II levels, decreases vascular tone and aldosterone secretion. Reduces mortality	Heart failure, hypertension, diabetes	Oral; short half-life but large doses used Duration: 12–24 h	Cough, renal damage, hyperkalemia, contraindicated in pregnancy
Benazepril, enalapril, others: like captopril *Losartan, candesartan, others*: angiotensin receptor blockers (see Chapter 11); benefits not documented as well as those of ACE inhibitors *Sacubitril*: Neprilysin inhibitor; increases BNP levels; used in combination with valsartan for heart failure				
Positive inotropic drugs				
Cardiac glycosides: digoxin	Inhibits Na^+/K^+ ATPase sodium pump and increases intracellular Na^+, decreasing Ca^{2+} expulsion and increasing cardiac contractility	Chronic heart failure, nodal arrhythmias	Oral, parenteral Duration: 40 h	Arrhythmogenic! Nausea, vomiting, diarrhea, visual, and endocrine changes (rare)
Sympathomimetics: dobutamine	$Beta_1$-selective sympathomimetic, increases cAMP and force of contraction	Acute heart failure	Parenteral Duration: a few minutes	Arrhythmias

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Beta blockers				
Carvedilol, metoprolol, bisoprolol	Poorly understood reduction of mortality, possibly by decreasing remodeling	Chronic heart failure	Oral Duration varies (see Chapter 10)	Cardiac depression (see Chapter 10)
Vasodilators				
Nitroprusside	Rapid, powerful vasodilation reduces preload and afterload	Acute severe decompensated failure	IV infusion Duration: a few minutes	Excessive hypotension • thiocyanate and cyanide toxicity
Hydralazine + isosorbide dinitrate	Poorly understood reduction in mortality	Chronic failure in African Americans	Oral	Headache, tachycardia
Nesiritide	Atrial peptide vasodilator, diuretic	Acute severe decompensated failure	Parenteral Duration: a few minutes	Renal damage, hypotension

Ang II, angiotensin II; *cAMP, cyclic adenosine monophosphate*.

Summary of drug treatment for CHF

Drug Group	Drugs	Beneficial Effects
Chronic failure (oral)		
Diuretics	Thiazides, furosemide, spironolactone	Reduced preload, afterload; spironolactone, reduced aldosterone effects
Cardiac glycoside	Digoxin	Positive inotropic effect
Vasodilators	Hydralazine, isosorbide dinitrate	Reduced preload, afterload
Angiotensin antagonists	Captopril, losartan	Reduced remodeling, preload, afterload, apoptosis
β blockers	Carvedilol, metoprolol	Reduced afterload, reduced remodeling, apoptosis
Acute failure (parenteral)		
Diuretics	Furosemide	Reduced pulmonary vascular pressures, preload
β_1 Agonists	Dobutamine	Increased cardiac force, output
Vasodilators	Nitroprusside, nitroglycerin	Reduced preload, afterload