Heart Faliure

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body

-Dyspnea

-Fatigue

-Fluid retention

- HF, may be due to :

✓ MI

✓ HTN

✓ Arteriosclerotic heart disease

✓ Congenital heart disease

- “Chronic activation of the sympathetic nervous system and the renin angiotensin-aldosterone axis is associated with remodeling of cardiac tissue, characterized by loss of myocytes, hypertrophy, and fibrosis”

Goals of pharmacologic intervention in HF

- ✓ Slow disease progression
- ✓ Increase survival
- ✓ Improve QOL.

PHYSIOLOGY OF MUSCLE CONTRACTION

➢ Action potential:

- Generated by the “pacemaker” located in SA and AV node cells

➢ Cardiac contraction:

Regulated by Intracellular Ca levels (free Ca)

The higher intracellular Ca levels the more contraction occurs

Cardiovascular Consequences of HF

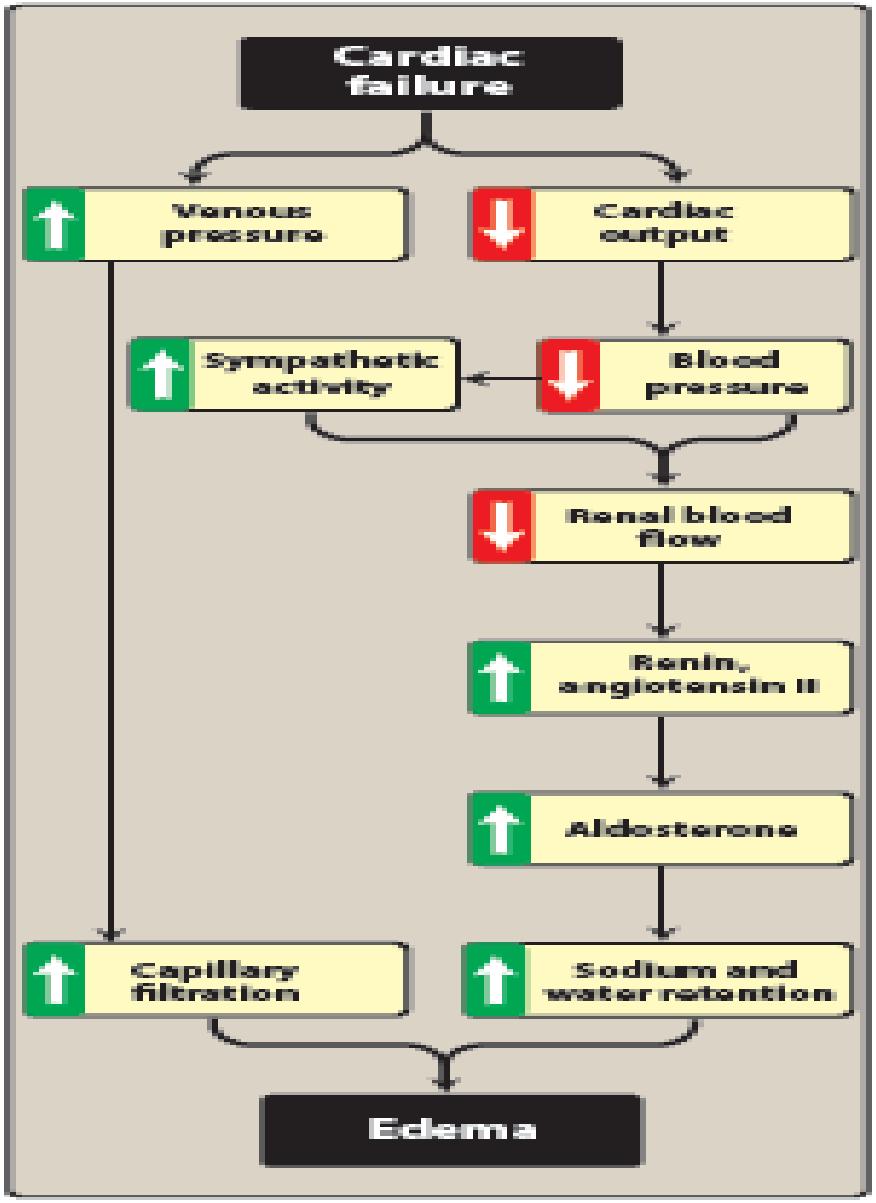


Figure 16.4
Cardiovascular consequences of heart failure.

Consequences of HF:

- Activation of the SNS (β-blockers)
- Activation of RAAS (ACEIs, ARBs)
- Myocardial Hypertrophy or dilated cardiomyopathy
- Increases blood volume (Duiretics)

THERAPEUTIC OBJECTIVES AND GENERAL MEASURES FOR CHRONIC HEART FAILURE

Therapeutic objectives in treating heart failure are
- to improve symptoms and
- to prolong survival.

General principles of treating heart failure:
- restrict dietary salt;
- if there is hyponatraemia, restrict fluid;
- review prescribed drugs and if possible, withdraw drugs that aggravate cardiac failure:
- some negative inotropes (e.g. **verapamil)**
- cardiac toxins (e.g. **daunorubicin, ethanol, imatinib, gefitinib, trastuzumab)**
- drugs that cause salt retention (e.g. NSAID).
- consider anticoagulation on an individual basis.

HF Pharmacology

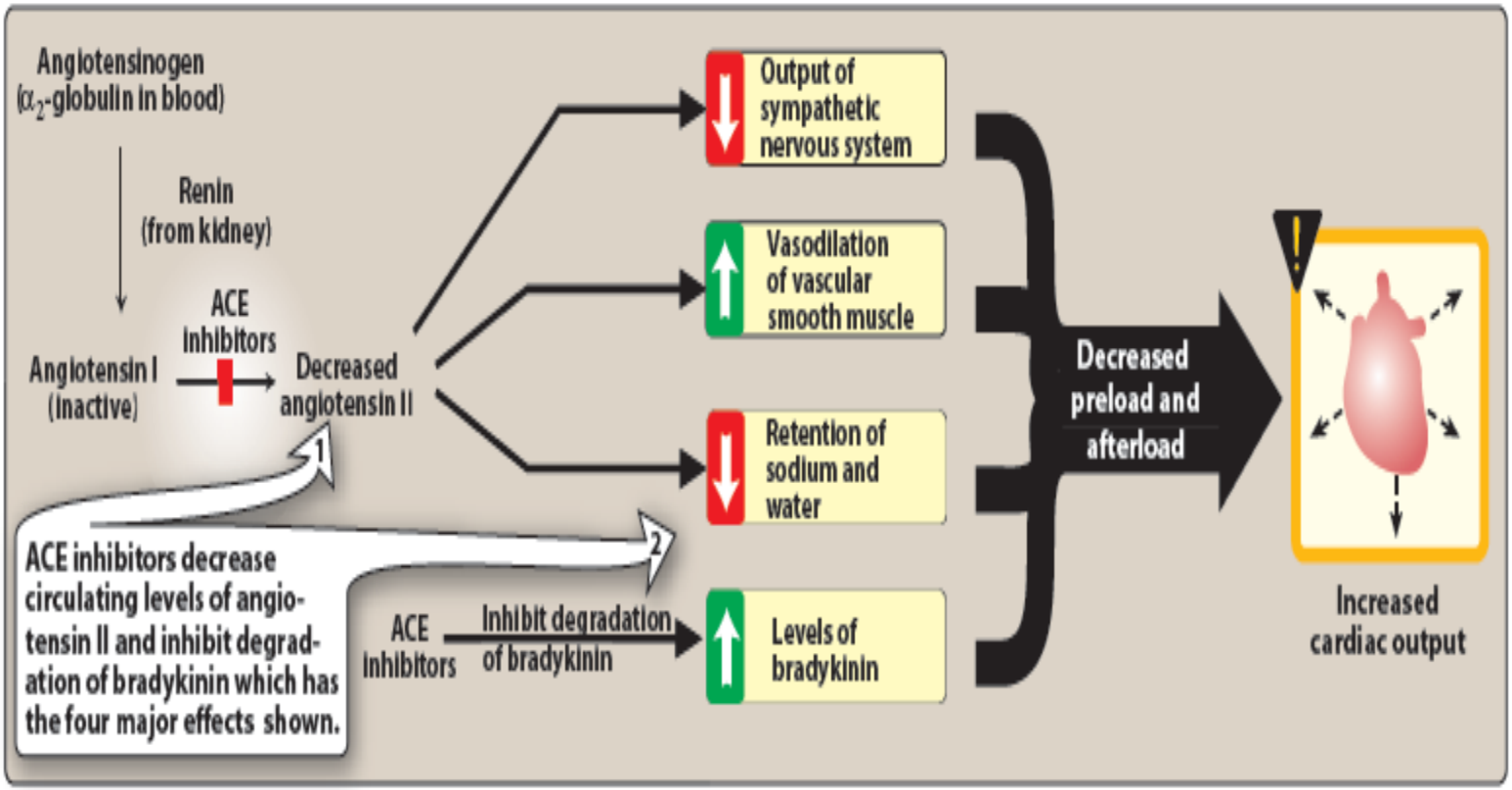
I. RAAS Inhibitors: *(ACEIs, ARBs)*
II. β-Blockers : *(Bisoprolol,Carvidolol, metoprolol)*
III. Duiretics : *(Thiazaides, Loop)*
IV. Digitalis glycosides

Angiotensin-converting enzyme inhibitors

- (ACE) inhibitors are the agents of choice in HF.
- These drugs:

1. Block the enzyme that cleaves angiotensin I to formthe potent vasoconstrictor ***angiotensin II (vasoconstictor)***
2. Maintain the activation of ***Bradykinis (vasodilator)***
3. Decrease **Aldosterone** secretion

"ACE inhibitors may be considered for single-agent therapy in patients who present with mild dyspnea on exertion and do not show signs or symptoms of volume overload (edema)"


Angiotensinogen
(α_2-globulin in blood)
Renin
(from kidney)
ACE
inhibitors
Angiotensin I
(inactive)
Decreased
angiotensin II
1
2
ACE inhibitors decrease circulating levels of angiotensin II and inhibit degradation of bradykinin which has the four major effects shown.
ACE
inhibitors
Inhibit degradation
of bradykinin
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Retention of
sodium and
water
Levels of
bradykinin
Decreased
preload and
afterload
Increased
cardiac output

Combinations

- ACE inhibitors may be used in combination with:

- Diuretics,
- β-blockers,
- *Digoxin,*

Pharmacokinetics

- Better taken on empty stomach
- All are prodrugs except *captopril*
- Require activation by hydrolysis via hepatic enzymes
- Plasma half-lives of active compounds vary from 2 to 12 hours
- *Ramipril Q24 hrs (newer)*

Adverse effects

- 1st dose hypotension
- renal insufficiency
- Hyperkalemia
- Angioedema
- **Persistent dry cough**

Angiotensin-receptor blockers

- ✓ Orally active compounds that are extremely potent competitive antagonists of the

"Angiotensin Type 1 receptor **AT1**".

- ✓ One advantage over ACEIs is that they produce complete blockade i.e (more potenet than AngII itself on the AT1 receptor)
- ✓ BUT they don't up-regulate Bradykinin
- ✓ (NO cough)**

losartan, candesartan, irbesartan, valsartan

"All the ARBs are approved for treatment of hypertension based on their clinical efficacy in lowering blood pressure and reducing the morbidity and mortality associated with hypertension. As indicated above, their use in HF is as a ***substitute for ACE inhibitors*** in those patients with ***severe cough or angioedema"***

Pharmacokinetics

- orally active
- once-a-day dosing
- Extensive 1st pass effect
- **Losartan** (Prototype) has an active metabolite
- Excreted in urine and feces
- All are highly plasma protein bound (>90%) except for ***Candesartan***

Adverse effects of Sartans

- Similar to ACEIs
- NO cough

β-BLOCKERS

- If the heart is failing to pump already why to use Beta-Blocker?? !!!
- The rational behind their use is :

1. Chronic SNS activation
2. Chronic RAAS activation

✓ Despite their initial exacerbation of symptoms, however they:

- Improve mortality rate
- Reverse cardiac remodelling
- Improves systolic functioning

NOT ALL β-BLOCKERS!!!

- Some of β-BLOCKERS are approved in HF, these include:

✓ Carvidolol:

- *Non selective β-BLOCKER*
- *Has α-blocking activity*

✓ Metoprolol:

- β1-selective antagonist

✓ Bisoprolol

Treatment should be started at low doses and gradually titrated

Side effects

- **Intolerance : fatigue, cold extremities, erectile dysfunction;less commonly vivid dreams.**
- **Airways obstruction**
- **Hypoglycaemia**
- **Heart block –**
- **Metabolic disturbance**

DIURETICS

- ✓ A diuretic is used to control symptomatic **oedema** and **dyspnoea** in patients with heart failure
- ✓ A thiazide diuretic may be helpful in mild cases,
- ✓ Loop diuretics (Furosemide) is more potent and is more used
- ✓ Diuretics decrease both the “preload” and the “afterload”.

DIRECT VASODILATORS

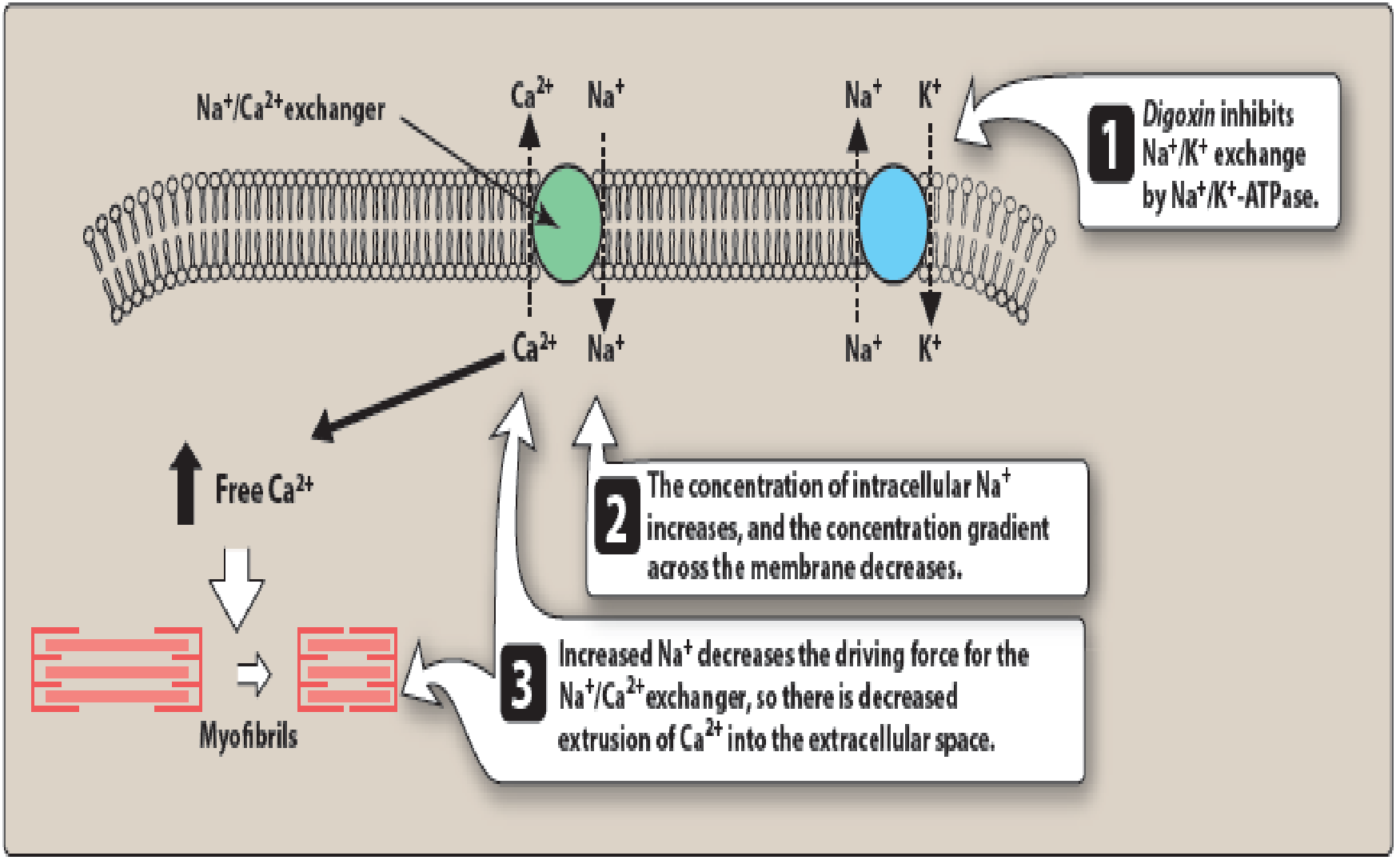
- Used if ACEIs,ARBs and Beta-Blockers are intolerated
- When more vasodilation is needed
- Hydralazine (arterial dilator) is combined with Isosorbide dinitrate (venous dilation), these 2 drugs together decrease afterload and preload.

INOTROPIC DRUGS

Digitalis glycosides

- ❖ "The inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle."
- The cardiac glycosides are often called digitalis or digitalis glycosides,because most of the drugs come from the digitalis (foxglove) plant
- They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are widely used in treating HF.

MOA: **Regulation of cytosolic calcium concentration**



Digitalis glycosides

- Increases the force of cardiac contraction
- Decrease in end-diastolic volume
- improved circulation leads to reduced sympathetic activity
- Reduction in heart rate
- *Digoxin slows down conduction velocity through the AV* node, which accounts for its use in atrial fibrillation

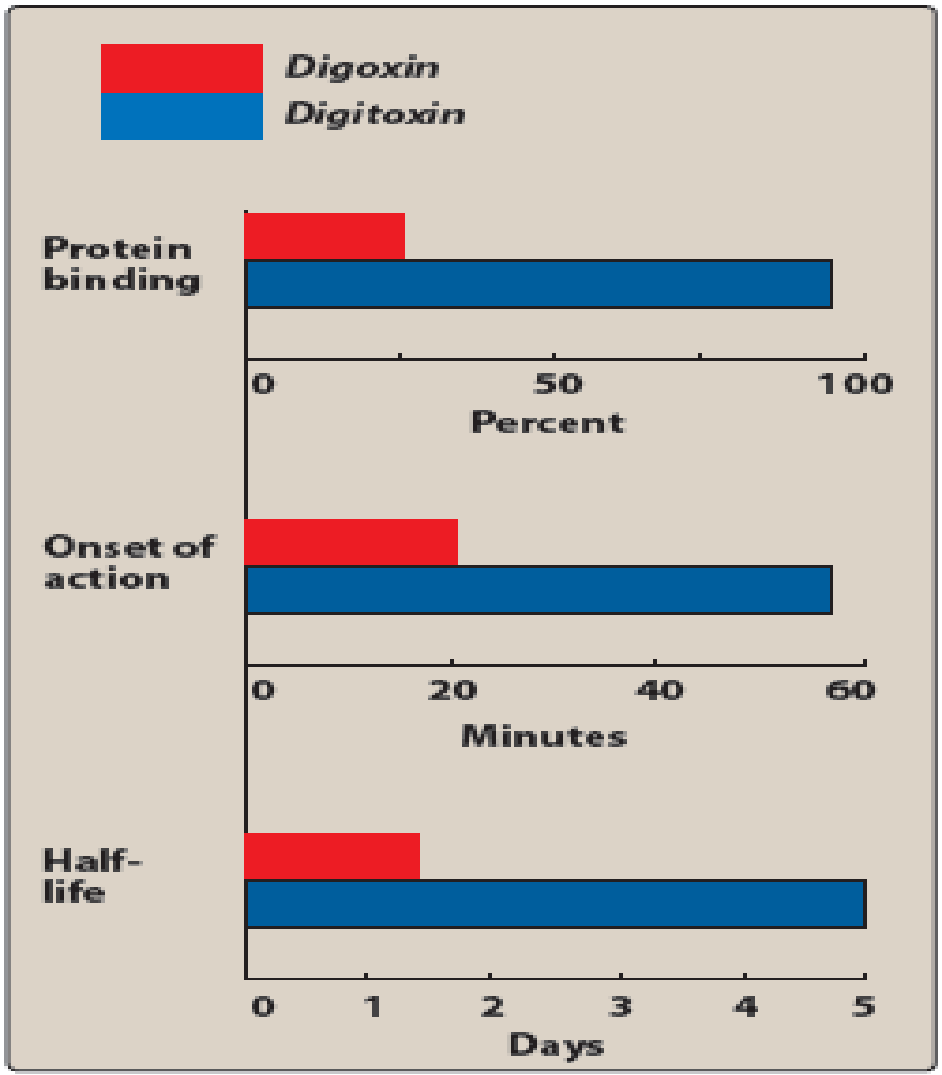
Therapeutic uses

- *Digoxin therapy is indicated in patients with* **severe** left ventricular systolic dysfunction after initiation of ACE inhibitor and diuretic therapy.
- *Digoxin's major indication is HF* with atrial fibrillation

Digitalis glycosides share the same effects but differ I potency and kinetics. Digoxin is the used one.

Digoxin is:
-very potent
-narrow margin of safety
-long half-life of 36 hours
- Dose is calculated according to the weight

Digitoxin **has much longer half-life and is extensively metabolized in Liver (C/I) in hepatic disease**



Adverse effects

- In general,decreased serum levels of potassium predispose a patient to *digoxin* toxicity.
- *Digoxin levels must be closely monitored in the presence of* renal insufficiency
- The common cardiac side effect is arrhythmia, characterized by slowing of AV conduction associated with atrial arrhythmias.
- Anorexia, nausea, and vomiting
- **Alteration of color perception**

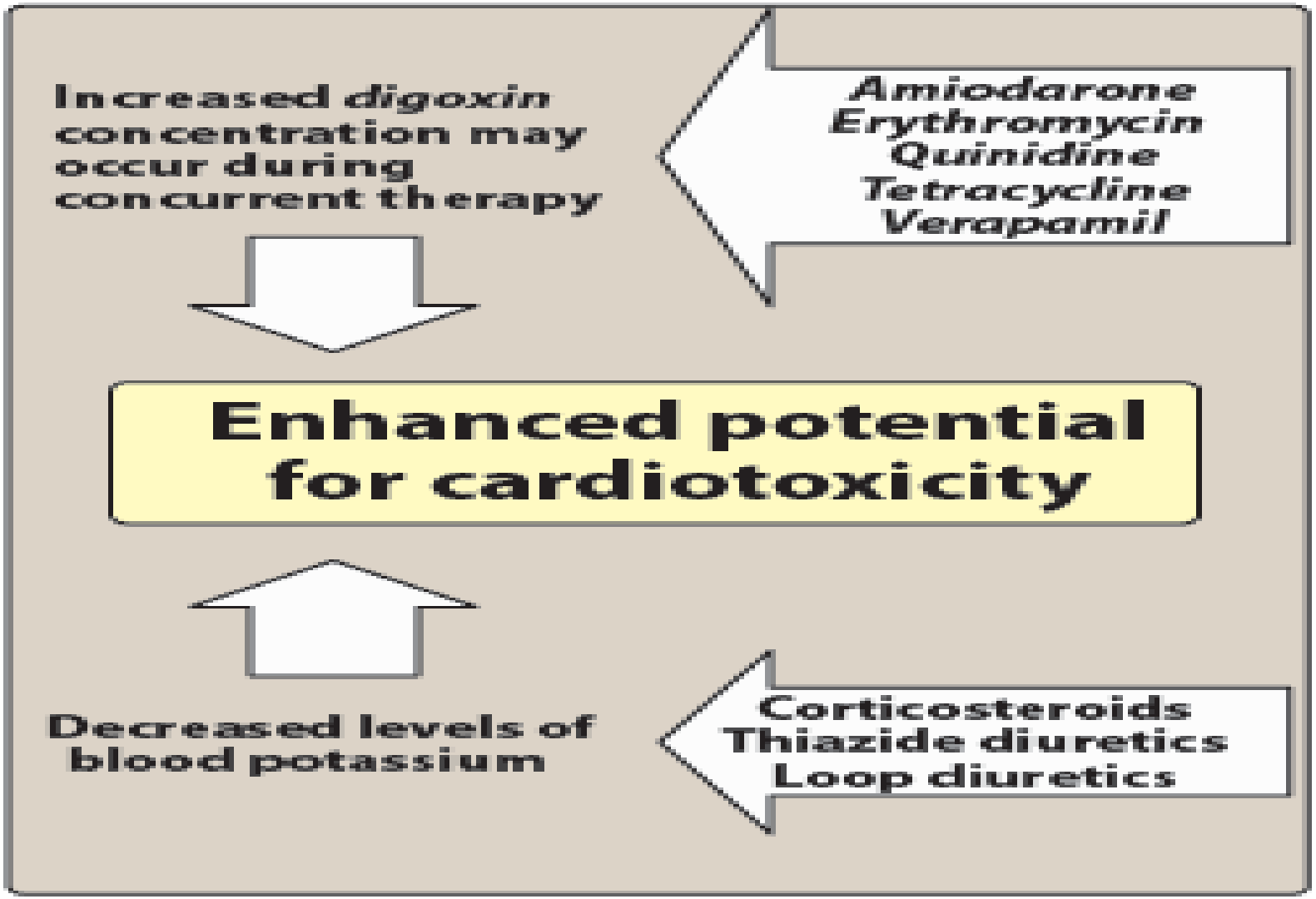


Figure 16.11
Drugs interacting with *digoxin*.

Digitalis Toxicity

- Digoxin toxicity is often divided into acute or chronic:
- **Chronic** intoxication is an extension of the therapeutic effect of the drug and is caused by excessive calcium accumulation in cardiac cells (calcium overload). This overload triggers **arrhythmias**.
- Severe, **acute** intoxication caused by suicidal or accidental extreme overdose results in **cardiac depression** leading to cardiac arrest rather than arrhythmias.

Digitalis Toxicity

- Treatment of digitalis toxicity includes several steps:

1) Correction of potassium or magnesium deficiency

- Correction of potassium deficiency (caused, eg, by diuretic use) is useful in chronic digitalis intoxication.
- Mild toxicity may often be managed by omitting 1 or 2 doses of digitalis and giving oral or parenteral K+ supplements.
- However, severe acute intoxication (as in suicidal overdoses) usually causes marked hyperkalemia (because of potassium loss from the intracellular compartment of skeletal muscle and other tissues). Acute digitalis intoxication should not be treated with supplemental potassium.

Digitalis Toxicity

- Treatment of digitalis toxicity includes several steps:

2) Antiarrhythmic Drugs

- Antiarrhythmic drugs are useful if arrhythmia is prominent and does not respond to normalization of serum potassium.
- Agents that do not severely impair cardiac contractility (eg, lidocaine or phenytoin) are favored.
- Severe acute digitalis overdose usually causes marked inhibition of all cardiac pacemakers, and an electronic pacemaker may be required. Antiarrhythmic drugs are dangerous in such patients.

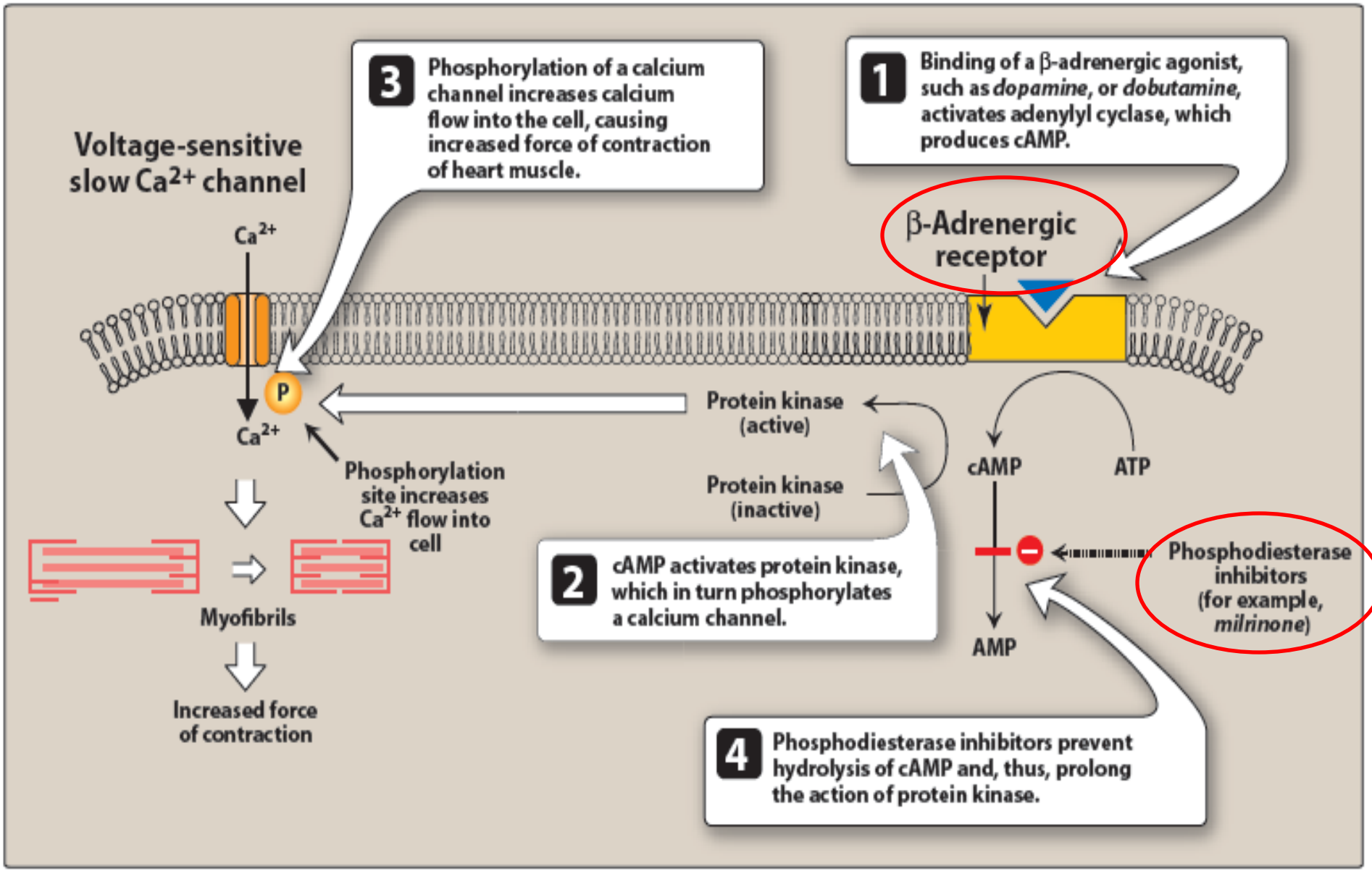
Digitalis Toxicity

- Treatment of digitalis toxicity includes several steps:

3) Digoxin Antibodies

- Digoxin antibodies (**digoxin immune fab; Digibind)** are extremely effective and should always be used if other therapies appear to be failing.
- They are effective for poisoning with many cardiac glycosides in addition to digoxin and may save patients who would otherwise die.

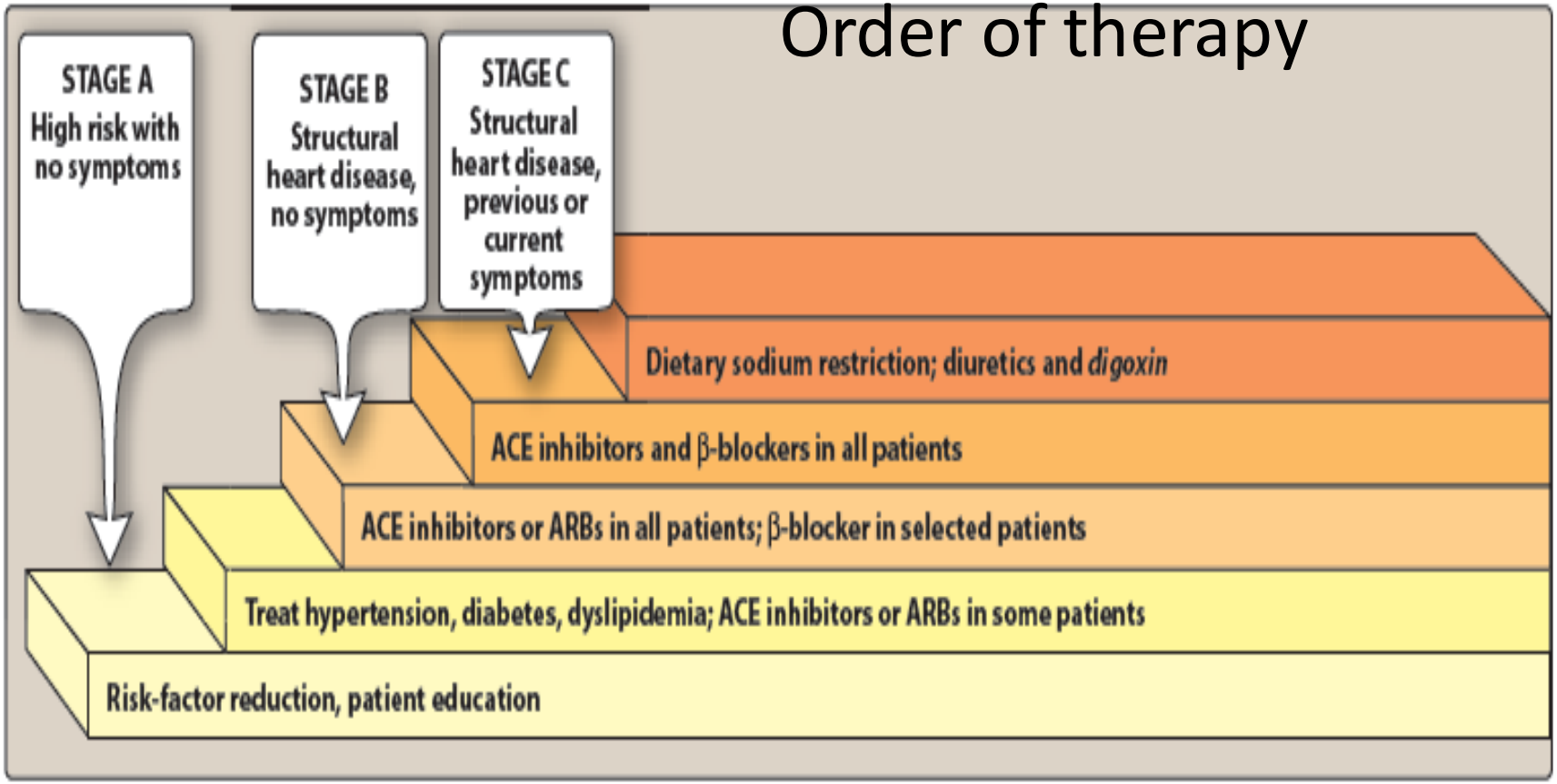
OTHER INOTROPS:

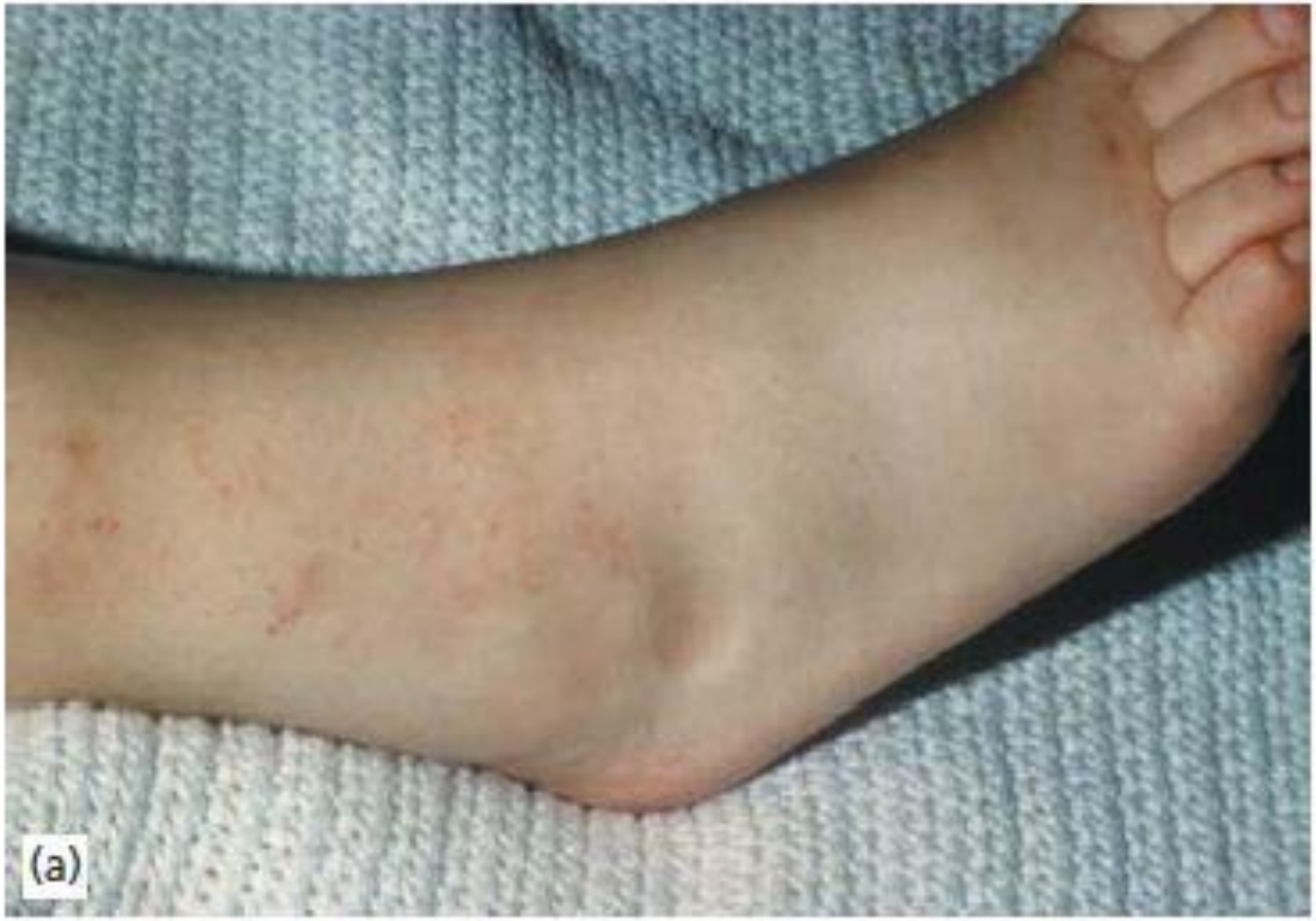


ALDOSTERONE ANTAGONISTS

Spironolactone (or the newer expensive agent, eplerenone), when added to conventional therapy with loop diuretic, and β-adrenoceptor antagonist, further improves survival. Concerns regarding hyperkalaemia in such patients may have been overstated, at least provided patients with appreciably impaired renal function are excluded from such treatment

Order of therapy




(a)