Heart failure

- 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

- Main symptoms:
  - Dyspnea
  - Fatigue
  - Fluid retention

- HF is caused by the impaired ability of the heart to adequately fill with and/or eject blood

- HF is accompanied by abnormal increases in blood volume and interstitial fluid, that's why it is called Congestive heart failure
- Dyspnea occurs from pulmonary congestion in left HF
- Peripheral edema occurs in right HF

- Causes of HF:
  - Arteriosclerotic heart disease
  - Myocardial infarction
  - Hypertensive heart disease
  - Valvular heart disease
  - Dilated cardiomyopathy
  - Congenital heart disease

- Left systolic dysfunction secondary to coronary artery disease is the most common cause of HF (70% of cases)

Compensatory physiological responses in HF

- The failing heart evokes three major compensatory mechanisms to enhance cardiac output

1. Increased sympathetic activity

2. Activation of the renin–angiotensin–aldosterone system

3. Myocardial hypertrophy

- Although initially beneficial, they ultimately result in further deterioration of cardiac function

HF

- Physiologic compensatory mechanisms in HF
  - Chronic activation of the sympathetic nervous system and renin angiotensin-aldosterone system is associated with remodeling of cardiac tissue
    - Loss of myocytes, hypertrophy, fibrosis.
  - This interferes with the ability of the heart to pump blood efficiently
  - Additional neurohormonal pathways are activated worsening the situation and if left untreated can lead to death

Compensatory physiologic mechanisms in HF

- Increased sympathetic activity
  - Baroceptors sense a decrease in blood pressure and activate the sympathetic nervous system to increase tissue perfusion
  - This leads to increased heart rate and a greater force of contraction of the heart muscle
  - The resulting vasoconstriction enhances venous return and increases cardiac preload
  - All this increases the work of the heart leading to further decline in cardiac function

Compensatory physiologic mechanisms in HF

- Activation of the renin angiotensin system
  - Reduced cardiac output decreases blood flow to the kidney promoting the release of renin
  - This increases the formation of angiotensin II and release of aldosterone
  - The peripheral resistance (after load) increases, and the sodium and water retention is promoted
  - Blood volume increases, more blood volume is returned to the heart (preload)
  - If the heart is unable to pump this extra volume, venous pressure increases causing peripheral and pulmonary edema
  - All this increases the work of the heart, causing further decline in cardiac function

Compensatory physiologic mechanisms in HF

- Myocardial hypertrophy
  - The heart increases in size and the chambers dilate
  - Initially stretching of the heart leads to stronger contraction
  - Excessive elongation of the fibers results in weaker contractions and diminishes the ability to eject blood (systolic failure, the ventricles do not pump blood efficiently)
  - Diastolic failure occurs when the ability of the ventricles to relax and accept blood is impaired by structural changes like hypertrophy, the ventricle does not fill adequately

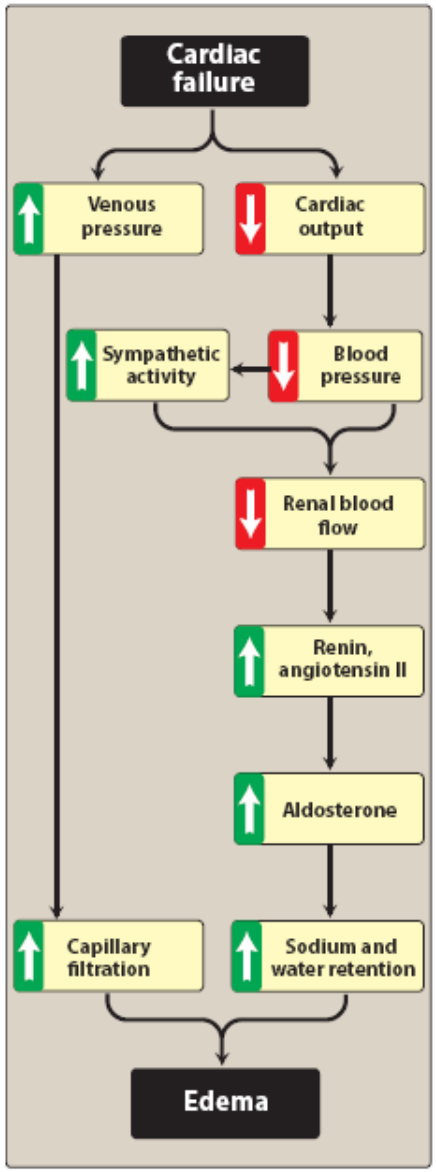


Figure 19.4
Cardiovascular consequences of HF.

Compensatory physiologic mechanisms in HF

- If the compensatory mechanisms adequately restore cardiac output the HF is said to be **compensated**

- The compensation increases the work of the heart and contributes to further decline in cardiac performance

- If the compensatory mechanisms fail to maintain cardiac output, HF is **decompensated**

Pharmacological treatment of HF

- Goals of HF therapy
  - Alleviate symptoms
  - Slow the disease progression
  - Improve survival
- Drug classes used in HF
  1. Angiotensin-converting enzyme inhibitors
  2. Angiotensin receptor blockers
  3. Aldosterone antagonists
  4. β-Blockers
  5. Diuretics
  6. Direct vaso- and venodilators
  7. Inotropic agents

Pharmacological treatment of HF

- Individuals might have one or more of the drug classes used for HF depending on the severity of the disease

- Beneficial effects of HF treatment
  - Reduction of the load on the heart
  - Decrease in extracellular fluid volume
  - Improved cardiac contractility
  - Slowing the rate of cardiac remodeling

- Non-pharmacological strategies for HF
  - Fluid limitations (less than 1.5 L to 2 L daily)
  - Reduction in physical activity
  - Low dietary intake of sodium <2000 mg/day

- Drugs that may exacerbate HF
  - Nonsteroidal anti-inflammatory drugs
  - Alcohol
  - Nondihydropyridine Calcium channel blockers
  - Some antiarrhythmic drugs

Renin-Angiotensin Aldosterone system

- HF activates the renin-angiotensin system by:
  - Promoting renin release in response to lower renal perfusion pressure caused by the failing heart
  - Sympathetic stimulation and activation of β receptors in the kidney leading to renin release
- The potent vasoconstrictor angiotensin II is produced
- The resulting stimulation of Aldosterone release causes salt and water retention increasing the preload and afterload that are characteristic of the failing heart
- High levels of angiotensin II and aldosterone have direct detrimental effects on the cardiac muscle causing remodeling and fibrosis

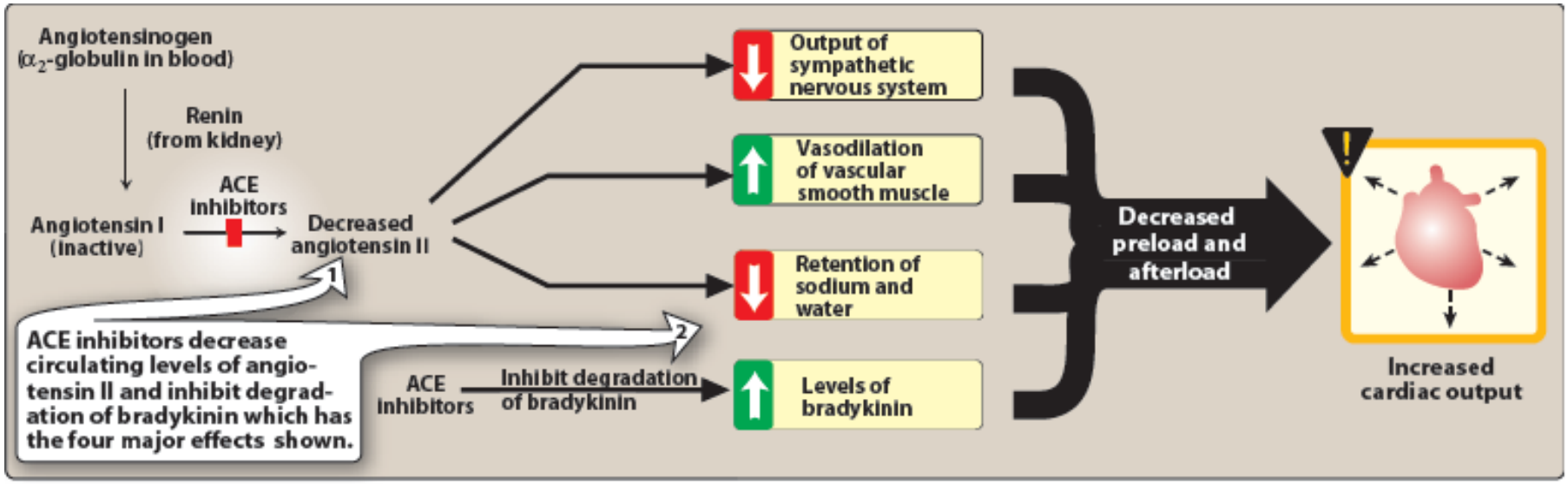
Inhibitors of the renin angiotensin aldosterone system

- Angiotensin converting enzyme inhibitors
- Angiotensin receptors blockers

Angiotensin converting enzyme inhibitors

- Drugs of choice for HF

- Mechanism of action
  - Block the enzyme that converts angiotensin I to the potent vasoconstrictor angiotensin II
  - Inhibit degradation of bradykinin causing vasodilation
  - Decrease aldosterone secretion decreasing sodium and water retention


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

Angiotensin converting enzymes inhibitors

- Captopril
- Enalapril
- Fosinopril
- Lisinopril
- Quinapril
- Ramipril

Angiotensin converting enzyme inhibitors

- Beneficial effects on heart
  - Reduce vascular resistance (afterload), venous tone (preload) and blood pressure
  - Increase cardiac output

- The use of ACE inhibitors significantly decreases morbidity and mortality in patients with congestive heart failure
- Can be used in combination with β-lockers, digoxin, aldosterone-antaonist, hydralazine/isosorbide

ACE inhibitors

- Can be used for single agent therapy in patients with mild dyspnea on exertion and no volume overload (no edema)
- Depending on the severity of the HF, ACE inhibitors can be used in combination with diuretics, β-blockers, digoxin and aldosterone antagonists
- ACE inhibitors are beneficial for patients with recent MI

ACE inhibitors

- Taken on empty stomach because presence of food decreases absorption
- All are prodrugs except captopril and require activation by hydrolysis by liver enzymes

Angiotensin converting enzymes inhibitors

- Adverse effects
  - Postural hypotension
  - Renal insufficiency
  - Hyperkalemia
  - Angioedema
  - Persistent dry cough

- Contraindicated in pregnancy

Angiotensin receptor blockers (ARBs)

- Losartan
- Candesartan
- Valsartan
- Temisartan

- Competitive antagonists of angiotensin receptor

- Used for HF in patients who can not tolerate angiotensin converting enzyme inhibitors (when dry cough occurs)

Angiotensin receptor blockers (ARBs)

- Lower blood pressure and reduce the morbidity and mortality associated with hypertension
- Adverse effects: similar to ACE inhibitors, but do not cause dry cough
- Contraindicated in pregnancy

β-blockers

- Two β-blockers are approved for use in HF
  - Metoprolol (β1 antagonist)
  - Carvediol (blocks α and β)
- Block the changes caused by chronic activation of the sympathetic nervous system
- Decrease heart rate and inhibit the release of renin
- Decrease remodeling of cardiac muscle fibers caused by norepinephrine, reduce hypertrophy and cell death
- Treatment is started with low doses that are slowly increased to optimal levels
- Beneficial if HF is accompanied by hypertension in the patient
- Not recommended in acute heart failure or in high risk patients with no symptoms

Diuretics

- Thiazide and loop diuretics
- Bumetanide
- Furosemide
- Metalazone
- Hydrochlorothiazide
- Thiazide diuretics are mild, loop diuretics are the most commonly used diuretics in HF

Diuretics

- Relieve pulmonary congestion and peripheral edema
- Reduce symptoms of volume overload including orthopnea and paroxysmal nocturnal dyspnea
- Decrease plasma volume and venous return to the heart (preload), this decreases cardiac workload and oxygen demand
- Can decrease afterload by reducing plasma volume, and so reduce blood pressure

Direct acting vasodilators

- Hydralazine
- Isosorbide dinitrate
- Isosorbide mononitrate

- Cause vasodilation leading to reduced cardiac preload

- Used if patient is intolerant to ACE inhibitors or β-blockers

Inotropic drugs

- Inotropic agents are reserved for acute HF signs and symptoms in mostly the inpatient setting
- Positive inotropic agents enhance cardiac muscle contractility and increase cardiac output
- The positive inotropic action is the result of increased cytoplasmic Ca^{2+} ions through different mechanisms
- Inotropic drugs include:
  - Digitalis glycosides
  - β-Adrenergic agonists
  - Phosphodiesterase inhibitors
  - Some antiarrhythmic drugs

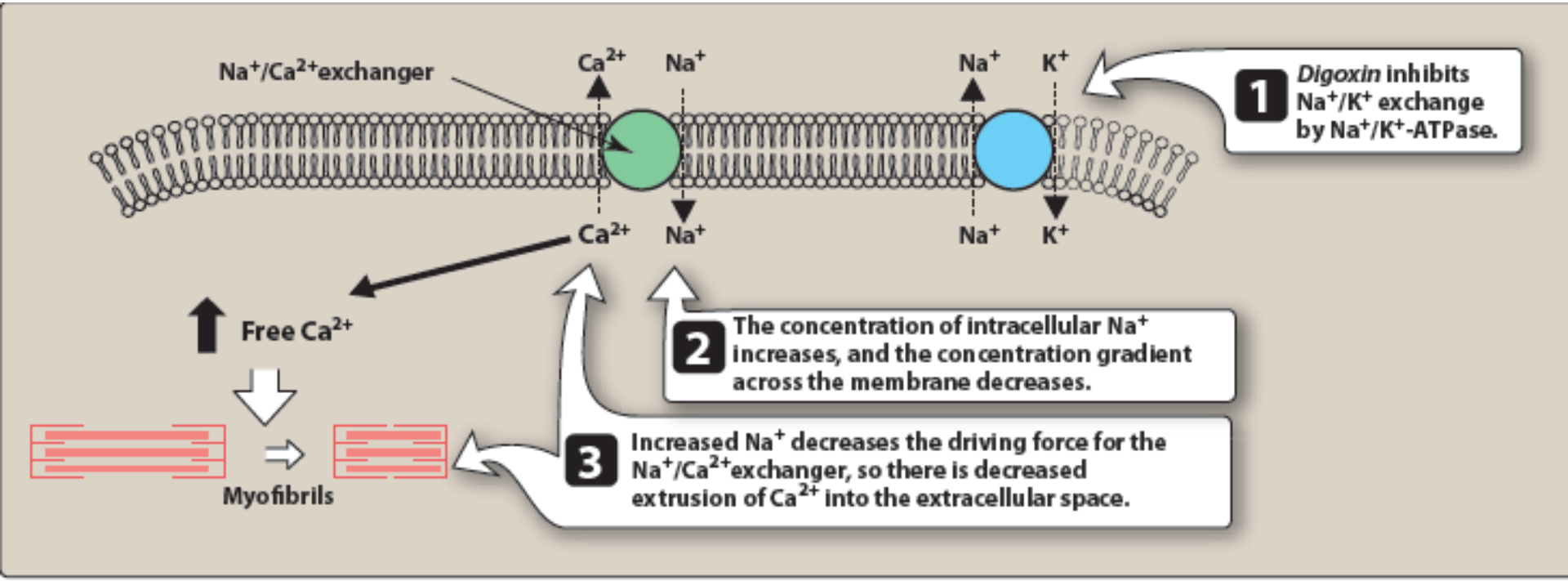
Digitalis glycosides

- Come from the digitalis (foxglove) plant
- Widely used for treatment of HF because they can increase the cardiac contractility by influencing sodium and calcium flow in the cardiac muscle
- Have a narrow therapeutic index
  (show a small difference between the therapeutic and toxic doses and can be fatal)
- The most widely used digitalis glycoside is Digoxin

Mechanism of action of Digoxin

- Digoxin inhibits Na^+/K^+ ATPase pump
- This decreases the Na^+ concentration gradient decreasing the ability of $Na^+/Ca2^+$ exchanger to move Ca^{2+} out of the cell
- The higher intracellular Na^+ is exchanged for extracellular Ca^{2+} by the Na^+/Ca^{2+} exchanger increasing intracellular Ca^{2+}
- This increases the free Ca^{2+} available for the contraction cycle of the cardiac muscle and enhances contractility

Mechanism of action of Digoxin



Digoxin

- Increases the force of cardiac contraction causing the cardiac output to be closer to that of the normal heart
- Increased myocardial contraction decreases end diastolic volume increasing the efficiency of contraction
- This improves circulation and hence reduces sympathetic activity, leading to lowered peripheral resistance and reduction in heart rate and cardiac oxygen demand

Digoxin

- Therapeutic uses
  - Severe left ventricular systolic dysfunction after initiation of ACE inhibitors and diuretic therapy
  - HF with atrial fibrillation

- Digoxin is eliminated by the kidney and might require dose adjustment based on kidney functions

- Digoxin adverse effects
  - Arrhythmia
    - Due to decrease in intracellular potassium
    - Also when the Na^+/K^+ ATPase pump is inhibited for a long term, the resting membrane potential may increase from -90mV to -70mV making the membrane more excitable and increasing the risk of arrhythmias
  - GI effects: anorexia, nausea, vomiting
  - CNS effects: headache, fatigue, confusion
- In case of digoxin toxicity,
  - Discontinue the drug
  - Administer K^+ supplements
  - Sometimes the antibody *digoxin immune Fab* should be used which binds to digoxin and inactivates it

Inotropic drugs

- Dobutamine (β-agonist)
- Cause positive inotropic effect and vasodilation
- Enhance cardiac muscle contractility and thus increase cardiac output
- Dobutamine increases intracellular cAMP which activates protein kinase that phosphorylates the slow Ca channels, increasing the entry of Ca into the myocardial cells and enhancing contraction
- Given IV in the hospital to treat acute HF

Inotropic drugs

- Phosphodiesterase inhibitors
- Milrinone
  - Used IV in patients with refractory HF for a short term
- Mechanism: increase the concentration of cAMP leading to an increase in intracellular Ca and enhancement of cardiac contractility

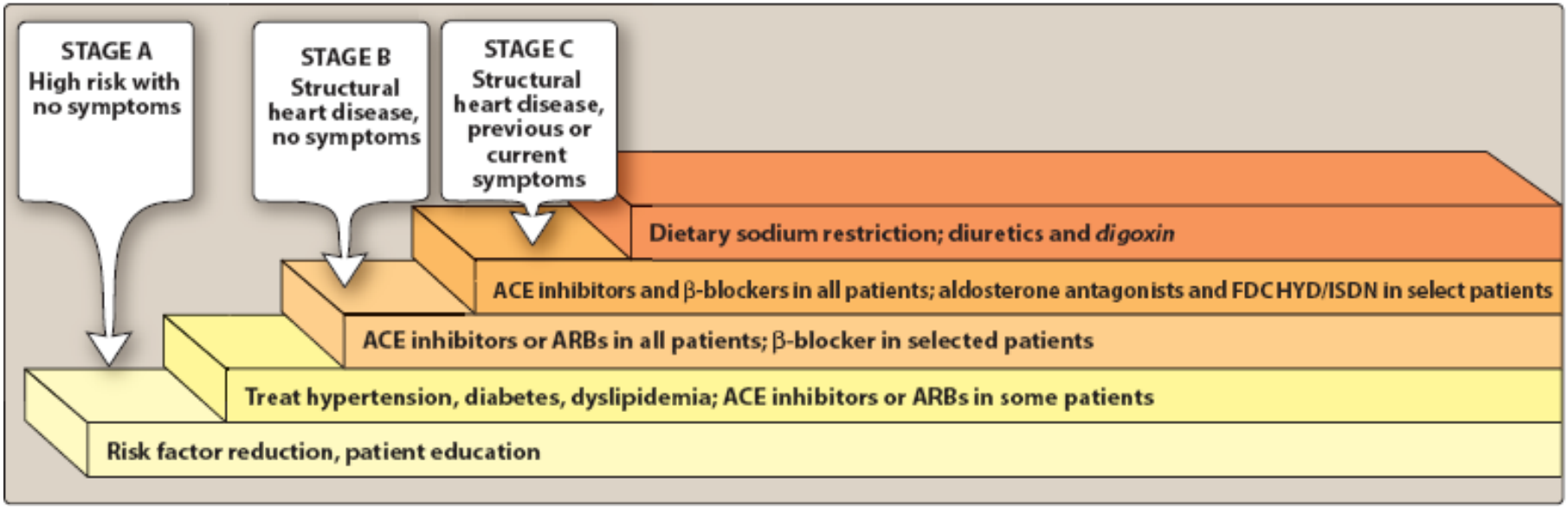
Aldosterone antagonists

- Spironolactone
- Mechanism of action
  - Direct antagonist of aldosterone
  - Prevents salt retention, myocardial hypertrophy and hypokalemia
- Used for the most advanced stages of HF where patients have elevated levels of aldosterone due to angiotensin II stimulation and low hepatic clearance of the hormone
- Adverse effects
  - GI disturbances (ulcer)
  - CNS abnormalities (confusion, lethargy)
  - Endocrine abnormalities (gynecomastia, decreased libido, menstrual irregularities)

Aldosterone antagonists

- Eplerenone
- Competetive antagonist of aldosterone at the mineralocorticoid receptor
- Similar action to spironolactone on the aldosterone receptor
- Lower incidence of endocrine related side effects due to its lower affinity for glucocorticoid, androgen and progesterone receptors

Order of therapy



Antiarrhythmics

Automaticity: The ability of some heart myocytes to intrinsically generate rhythmic action potentials in the absence of external stimuli

These myocytes are referred to as pacemakers, they show a slow spontaneous depolarization during diastole caused by inward positive current by sodium and calcium flow

The depolarization is fastest in the sinoatrial (SA) node (the initiation site of action potential) and it decreases as it goes through the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinjee system

Arrhythmias

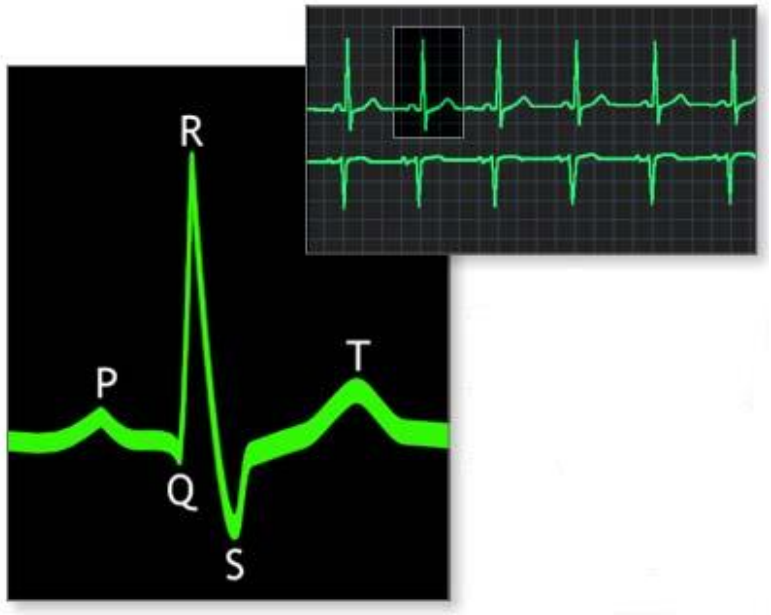
- Abnormalities in impulse generation and conduction in the myocardium
- They are presented with various symptoms
  - Bradycardia (slow heart rate) or tachycardia (rapid heart rate)
  - Heart could be beating regularly (sinus bradycardia, or sinus tachycardia) or irregularly (atrial fibrillation)
- The name of the arrhythmia is based on the heart cavity where it originates ex: Atrial tachycardia (arrhythmia originating in the atria)
- Arrhythmias can be divided into subgroups based on electricardiogram (ECG) findings

Arrhythmias

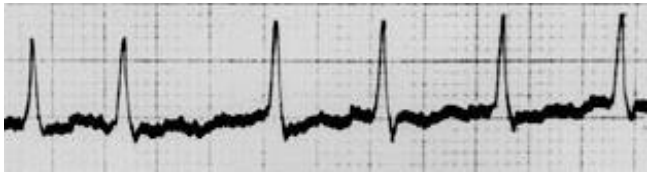
- Types of arrhythmias
  - Atrial arrhytmias
    - Atrial flutter
    - Atrial fibrillation
  - Supraventricular tachycardias
    - AV node reentry
    - Acute supraventricular tachycardia
  - Ventricular tachycardias
    - Acute ventricular tachycardia
    - Ventricular fibrillation

Normal Sinus Rhythm:

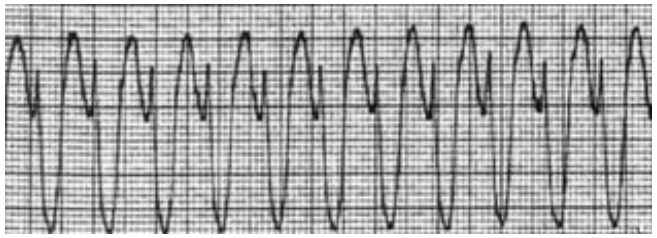
- P wave: Atrial depolarization
- QRS complex: Ventricular depolarization
- T wave: Ventricular repolarization



Abnormal Heart Rhythms



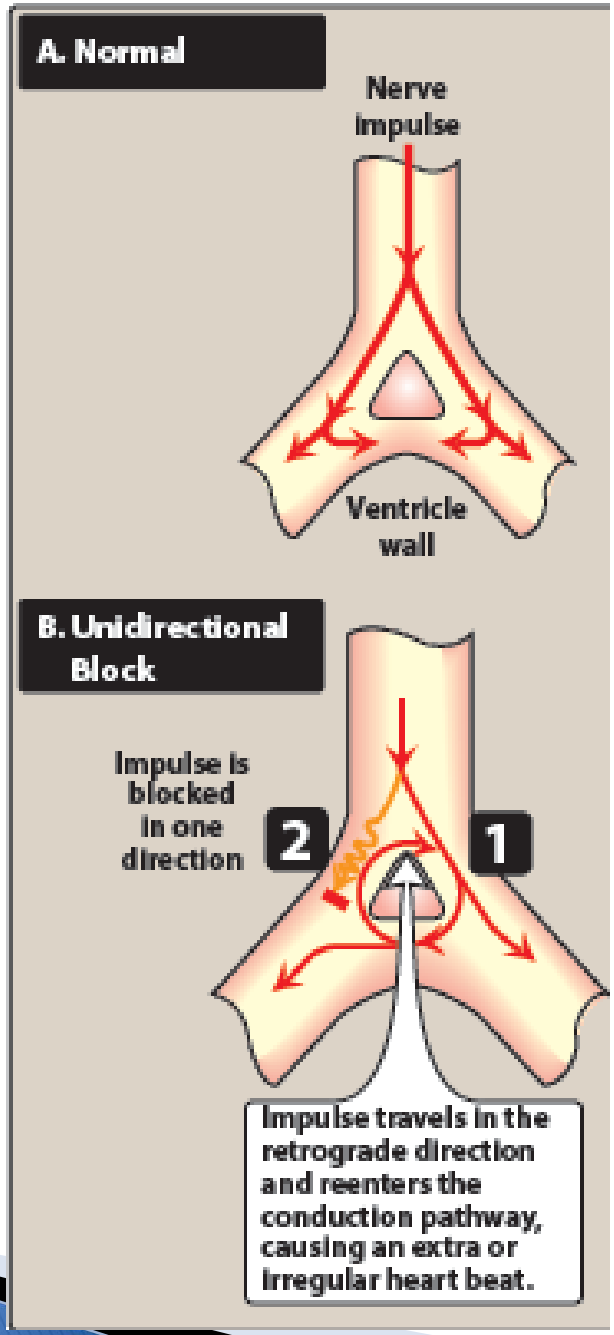
Atrial Fibrillation



Ventricular Tachycardia

Arrhythmias

- Causes of arrhythmias:
  - Abnormalities in impulse generation (abnormal automaticity)
    - If other cardiac myocytes other than SA node show automaticity, they may generate competing stimuli and cause arrhythmia
    - Damage to myocardial cells such as in hypoxia or potassium imbalance can cause abnormal automaticity
  - A defect in impulse conduction
    - Reentry: the most common cause of arrhythmias, it's an abnormal conduction pathway caused by a unidirectional block due to myocardial injury
    - This abnormal pathway results in re-excitation of ventricular muscle causing premature contraction or sustained ventricular arrhythmia


A. Normal
Nerve impulse
Ventricle wall
B. Unidirectional Block
Impulse is blocked in one direction
2
1
Impulse travels in the retrograde direction and reenters the conduction pathway, causing an extra or irregular heart beat.

Antiarrhythmic drugs

- Can modify impulse generation and conduction
- Suppress automaticity by blocking Na^+ or Ca^{2+} channels to reduce their ratio to K^+
- Prevent reentry by slowing conduction
- Many antiarrhythmic drugs have proarrhythmic actions and they can cause arrhythmia

Antiarrhythmic drugs

- Class I antiarrhythmics (Na^+ channels blockers)
- Class II antiarrhythmics (β-blockers)
- Class III antiarrhythmics (K^+ channel blockers)
- Class IV antiarrhythmics (Ca^{2+} channel blockers)
- Other antiarrhythmics

- Antiarrhythmic drugs are classified according to their predominant effect on the action potential
- Many of these drugs have actions relating to more than one class or have active metabolites with a different class of action

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Class I antiarrhythmic drugs

- Block voltage sensitive sodium channels and slow the rise of phase 0 of the action potential
- Decreased rate of entry of sodium slows the rate of rise of phase 0 of the action potential
- Decrease excitabitliy and conduction velocity
- Their use is declining due to their proarrhythmic effects especially in patients with reduced left ventricular functions and ischemic heart disease

Class I antiarrhythmic drugs

- Use-dependent (state-dependent):
  - These drugs bind more rapidly to open or inactiated sodium channels rather than to channels that are fully repolarized following recovery from the previous depolarization cycle
  - They show a greater degree of blockade in tissues that are frequently depolarizing (for example during tachycardia when sodium channels open frequently)
  - These drugs block cells that are discharging at an abnormal rate without interfering with the normal low frequency beating of the heart

Class I antiarrhythmics

- Subdivided into
  - Class IA
    - Have intermediate speed of association with activated/inactivated sodium channles and intermediate rate of dissociation from resting channels
    - Slow the rate of the rise of action potential (slow conduction)
    - Prolong action potential
    - Increase ventricular refractory period
    - Have concomitant class III activity
  - Class IB
    - Rapidly bind with sodium channels
    - Decrease the duration of the action potential by shortening repolarization
  - Class IC
    - Bind slowly to sodium channels
    - Depress the rate of rise of the membrane action potential
    - Slow conduction
    - Have little effect on the duration of the membrane action potential

Class I antiarrhythmics

- Proarrhythmic effect
  - Inhibition of potassium channels (Class III activity) widens the action potential leading to prolonged QT interval on ECG increasing the risk of developing life threatening ventricular tachyarrythmias (torsade de pointes)
  - QT prolongation is mostly drug induced but could also be genetic
  - Example on drugs causing QT prolongation
    - Quinidine
    - Erythromycin (antibiotic)
    - Imipramine (antidepressant)
  - Combining drugs with QT prolongation effect should be done with caution

Class I antiarrhythmic drugs

- Class IA
  - Quinidine
  - Procainamide
  - Disopyramide
- Class IB
  - Lidocaine
  - Mexiletine
  - Tocainide
- Class IC
  - Flecainide
  - Propafenone

Quinidine

- Prototype class IA drug
- Has concomitant Class III activity, can percipitate polymorphic ventricular tachycardia
  (torsade de pointes)
- Its clinical use is being replaced by Class IV
- Mechanism of action: binds to open and inactivated sodium channels and prevents sodium influx slowing the rapid upstroke in Phase 0 and decreases phase 4 spontanious depolarization. It also inhibits potassium channels, slowing conduction elocity and increasing refractoriness.

Quinidine

- Therapeutic uses
  - Used for a wide variety of arrhythmias
  - Atrial, AV-junctional and ventricular tachyarrhythmias
  - Used to maintain sinus rhythm after atrial flutter or fibrillation
  - Used to prevent frequent ventricular tachycardia
- Metabolized by P450 forming active metabolites
- Adverse effects
  - Nausea, vomiting, diarrhea
  - Arrhythmia (torsades de pointes)
  - SA and AV block or aystole
  - Ventricular tachycardia
  - Cinchonism (blurred vision, tinnitus, headache, disorientation, and psychosis)
  - Can increase the steady state concentration of digoxin

Procainamide

- Class IA drug
- Shows similar action as quinidine
- Has Class III drug properties
- Adverse effects
  - GI side effects are less frequent than with quinidine
  - Reversible lupus erythematosus
  - Asystole
  - Ventricular arrhythmias
  - CNS side effects (hallucination, psychosis)

Disopyramide

- Class IA drug
- Has class III activity
- Similar actions as quinidine
- Produces a negative inotropic effect
- Causes peripheral vasoconstriction
- Used for ventricular arrhythmias
- Adverse effects include anticholinergic side effects (dry mouth, urinary retention, blurred vision and constipation)

Lidocaine

- Class IB drug
- Local anesthetic
- Rapidly associate and dissociate from sodium channels
- Shortens Phase 3 repolarization and decreases the duration of action potential
- Useful for ventricular arrhythmias during myocardial ischemia such as with myocardial infarction
- Administered IV (not orally due to first pass effect)
- Adverse effects
  - Arrhythmia
  - CNS effects (drowsiness, confusion, agitation and convulsions)

Mexiletine and tocainide

- Class IB drugs
- Similar actions to lidocaine
- Can be administered orally
- Mexiletine is used for chronic treatment of ventricular arrhythmias associated with previous MI
- Tocainide is used for ventricular tachyarrhythmias
- Tocainide has pulmonary toxicity (can lead to cystic fibrosis)

Flecainide

- Class IC drug
- Slowly dissociate from resting sodium channels
- Therapeutic uses:
  - Refractory ventricular arrhythmias
  - Prevention of paroxysmal atrial fibrillation/flutter
  - Paroxysmal supraventricular tachycardia
- Actions: Suppress Phase 0 upstroke in Purkinje and myocardial fibers, slows conduction in cardiac tissue
- Has negative inotropic effect
- Adverse effects
  - Arrhythmia
  - Can induce life threatening ventricular tachycardia that is resistant to treatment

Propafenone

- Class IC drug
- Similar actions as flecainide
- Slows conduction in all cardiac tissues
- Broad spectrum antiarrhythmic drug

Class II antiarrhythmic drugs

- β- adrenergic antagonists

- Propranolol
- Metoprolol
- Esmolol

- Diminish phase 4 depolarization, depressing automaticity, prolonging AV conduction and decreasing heart rate and contractility

Class II antiarrhythmic drugs

- Used for:
  - Treatment of tachyarrhythmias caused by increased sympathetic activity
  - Treatment of atrial flutter and fibrillation and for AV nodal reentry tachycardia
- Propranolol
  - Reduces mortality due to sudden arrhythmia in post-myocardial infarction patients.
  - Can prevent ventricular arrhythmia
- Metoprolol
  - The most widely used β-blocker in cardiac arrhythmias
  - Lower risk of bronchospasm than with propranolol
- Esmolol:
  - Very short acting β-blocker.
  - Used IV in acute arrhythmias that occur during surgery or emergency

Class III antiarrhythmic drugs

- Block K^+ channels

- Amiodarone
- Dronedarone
- Sotalol

Class III antiarrhythmic drugs

- Block K^+ channels
- Diminish the outward potassium current during repolarization of cardiac cells
- Prolong the duration of action potential without altering Phase 0 of depolarization or the resting membrane potential. They prolong the effective refractory period

- All Class III drugs have the potential to induce arrhythmias

Class III antiarrhythmic drugs

- Amiodarone
  - Has Class I, II, III, and IV activity
  - Antiarrhythmic and antianginal
  - Prolongs the duration of action potential and the refractory period
  - The most commonly used antiarrhythmic
  - Used for
    - Severe refractory supraventricular and ventricular tachyarrhythmias
    - Atrial fibrillation
  - Adverse effects
    - GIT intolerance
    - Pulmonary fibrosis
    - Liver toxicity
    - Thyroid dysfunction

Class III antiarrhythmic drugs

- Dronedarone
  - Amiodarone derivative
  - Has Class I, II, III and IV actions
  - Adverse effects:
    - No thyroid dysfunction as with amiodarone
    - GIT side effects: nausea, vomiting and diarrhea

Class III antiarrhythmic drugs

- Sotalol
  - Also has potent non selective β-blocker activity
  - Blocks the rapid outward potassium current, prolonging repolarization and the duration of action potential, lengthening the effective refractory period
  - Used for long term therapy to decrease the rate of sudden death following acute MI
  - Adverse effects
    - Prolongation of QT interval (torsade de pointes) in 4% of patients

Class IV antiarrhythmic drugs

- Calcium channel blockers
  - Verapamil
  - Diltiazem

Class IV antiarrhythmic drugs

- Decrease the inward current carried by Ca^{2+} decreasing the rate of Phase 4 spontaneous depolarization
- Slow the conduction and prolong the effective refractory period in tissues that depend on Ca currents (AV node)
- Verapamil and diltiazem bind to open depolarized channels and prevent repolarization until the drug dissociates from the channel
- (Use dependent) they work most effectively when the heart is beating rapidly, in a normally paced heart, the calcium channels have time to repolarize and the bound drug dissociates from the channel before the next conduction pulse

Class IV antiarrhythmic drugs

- Used for hypertension, angina and arrhythmia
- More effective against atrial than ventricular arrhythmias
- Useful for treating reentrant supraventricular tachycardia and in reducing the ventricuar rate in atrial flutter and fibrillation
- Contraindicated in patients with depressed cardiac function, they have negative inotropic effect

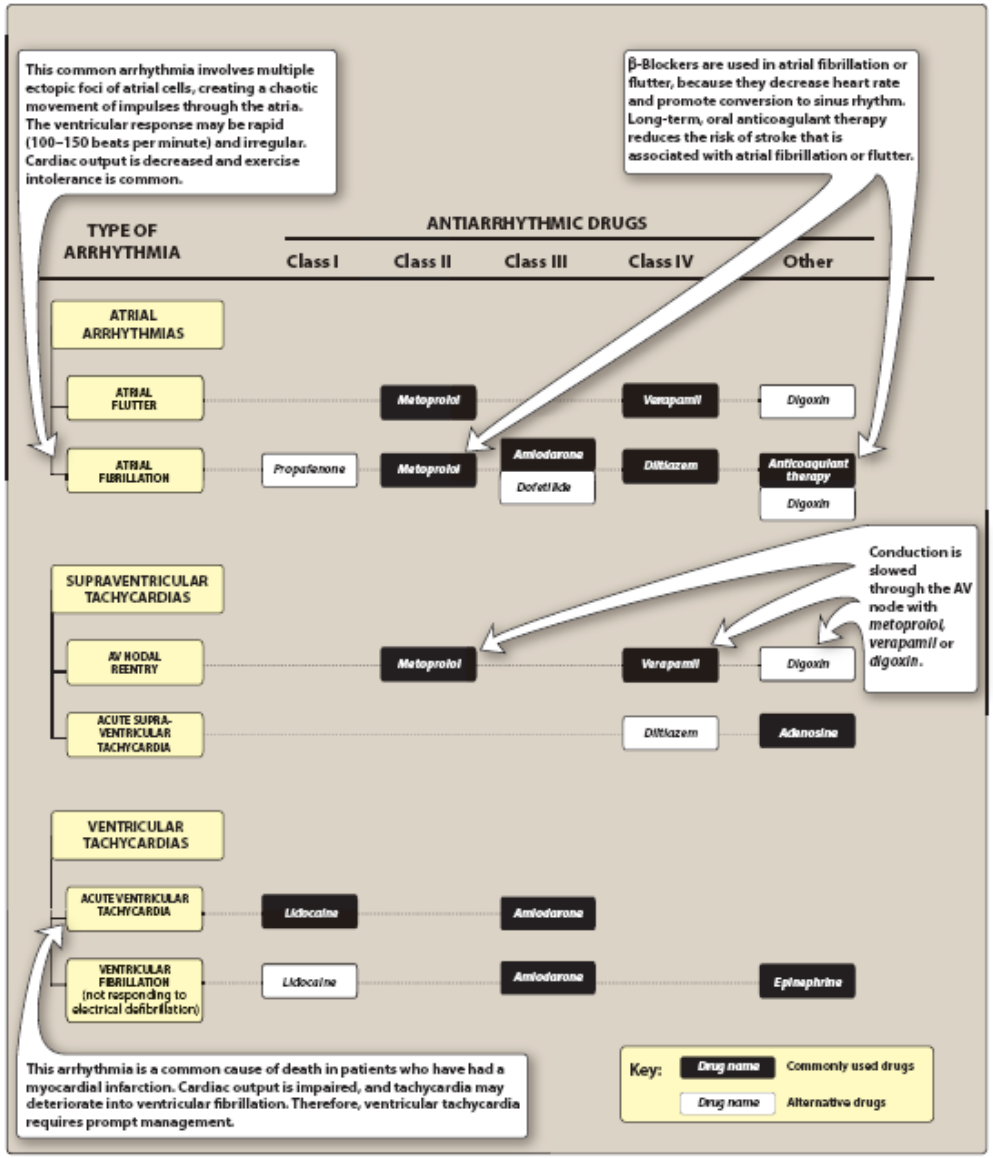
Other antiarrhythmic drugs

- Digoxin
  - Used for atrial fibrillation and flutter
  - Shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing the conduction velocity in the AV node
  - At toxic doses can cause ventricular tachycardia and fibrillation (treated with lidocaine)

- Adenosine
  - Naturally occurring nucleotide
  - At high doses, decreases conduction velocity, prolongs refractory period, and decreases automaticity in the AV node
  - Extremely short duration of action (15 seconds)
  - IV adenosine is used for acute supraventricular tachycardia
  - Has low toxicity, flushing, chest pain and hypotension

Other antiarrhythmic drugs

- Magnesium sulfate
  - Mg is necessary for transport of Na, Ca & K across cell membrane
  - Slows rate of SA node impulse formation
  - Prolongs conduction time along the myocardial tissue
  - Drug of choice for fatal arrhythmia torsade de pointes and digoxin-induced arrhythmia


This common arrhythmia involves multiple ectopic foci of atrial cells, creating a chaotic movement of impulses through the atria. The ventricular response may be rapid (100–150 beats per minute) and irregular. Cardiac output is decreased and exercise intolerance is common.
β-Blockers are used in atrial fibrillation or flutter, because they decrease heart rate and promote conversion to sinus rhythm. Long-term, oral anticoagulant therapy reduces the risk of stroke that is associated with atrial fibrillation or flutter.
TYPE OF ARRHYTHMIA
ANTIARRHYTHMIC DRUGS
Class I
Class II
Class III
Class IV
Other
ATRIAL ARRHYTHMIAS
ATRIAL FLUTTER
Metoprolol
Verapamil
Digoxin
ATRIAL FIBRILLATION
Propafenone
Metoprolol
Amiodarone
Dofetilide
Diltiazem
Anticoagulant therapy
Digoxin
Conduction is slowed through the AV node with metoprolol, verapamil or digoxin.
SUPRAVENTRICULAR TACHYCARDIAS
AV NODAL REENTRY
Metoprolol
Verapamil
Digoxin
ACUTE SUPRA-VENTRICULAR TACHYCARDIA
Diltiazem
Adenosine
VENTRICULAR TACHYCARDIAS
ACUTE VENTRICULAR TACHYCARDIA
Lidocaine
Amiodarone
VENTRICULAR FIBRILLATION (not responding to electrical defibrillation)
Lidocaine
Amiodarone
Epinephrine
This arrhythmia is a common cause of death in patients who have had a myocardial infarction. Cardiac output is impaired, and tachycardia may deteriorate into ventricular fibrillation. Therefore, ventricular tachycardia requires prompt management.
Key:
Drug name
Commonly used drugs
Drug name
Alternative drugs

Antianginal drugs

- Angina pectoris: a characteristic sudden severe pressing chest pain radiating to the neck, jaw, back and arms
- Caused by coronary blood flow insufficient to meet the oxygen demands of the myocardium, leading to ischemia
- Angina is caused by varying combinations of increased myocardial demand and decreased myocardial perfusion
- The imbalance between oxygen delivery and demand may result :
  - During exertion
  - From a spasm of the vascular smooth muscle
  - From obstruction of blood vessels by atherosclerotic lesions

Myocardial Ischemia and Angina

- Myocardial ischemia: Insufficient blood flow through coronary arteries to heart leading to imbalance between oxygen supply and demand
- Angina Pectoris: Choking and squeezing pain in the chest produced by ischemia
- Myocardial Infarction (MI): Extreme form of ischemia leading to significant cardiac tissue damage and cell death

Angina pectoris

- The transient episodes of myocardial ischemia do not cause cellular death as in MI
- Chronic ischemia may lead to deterioration in cardiac function causing:
  - Heart failure
  - Arrhythmias
  - Sudden death
- Life style modifications especially cessation of smoking are important in treatment of angina

Angina

- Sometimes surgery might be needed like
  - Angioplasty: A procedure used to for widening a narrowed or blocked coronary heart artery
  - Coronary artery bypass surgery which creates a new path for blood to flow to the heart and avoid the occluded area of the coronary artery

Types of angina

1. Effort induced angina, classic or stable angina

2. Unstable angina

3. Prinzmetal, variant vasospastic or rest angina

4. Mixed forms of angina

Effort induced angina, classic, typical or stable angina

- The most common type of angina.
- Characterized by a short lasting burning heavy or squeezing feeling in the chest.
- The pattern of chest pains and the amount of effort needed to trigger the chest pain do not change
- Caused by the reduction of coronary perfusion due to fixed obstruction of a coronary artery produced by atherosclerosis
- Due to the obstruction, the blood supply can not increase and the heart becomes venerable to ischemia whenever there is increased demand like physical activity
- Relieved by rest or nitroglycerin which decreases myocardial oxygen demand

Unstable angina

- Chest pain occurs with increased frequency, duration and intensity and is caused by progressively less effort

  (The most common cause of MI)
- Symptoms are not relieved with rest or nitroglycerin
- Requires hospital admission and therapy to prevent death and MI

Prinzmetal, variant vasospastic or rest angina

- Uncommon, occurs at rest
- It is due to sudden and unpredictable coronary artery spasm which decreases blood flow to the heart muscle
- Angina attacks are unrelated to physical activity, heart rate or blood pressure
- Responds well to coronary vasodilators like nitroglycerin and calcium channel blockers

Mixed forms of angina

- Patients with advanced coronary artery disease may have angina episodes during effort and during rest
- Presence of a fixed obstruction associated with endothelial dysfunction and vasospastic disease

Acute coronary syndrome

- An emergency situation
- Commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery
- If thrombus occludes most of the blood vessel and if the occlusion is untreated, necrosis of the cardiac muscle may occur (myocardial infarction)

Antianginal drugs

1. Organic nitrates
2. β-Blockers
3. Calcium channel blockers
4. Sodium channel blocker

- These drugs lower oxygen demand of the heart by affecting
  - Blood pressure
  - Venous return
  - Heart rate
  - Contractility

Organic nitrates

- Isosorbide dinitrate
- Isosorbide mononitrate
- Nitroglycerin

Organic nitrates

- Simple nitrates and nitrous acid esters of glycerol
- Cause a rapid reduction in myocardial oxygen demand followed by rapid relief of symptoms
- Effective in stable and unstable and variant angina pectoris

Organic nitrates

- Mechanism of action
  - Inhibit coronary vasoconstriction or spasm increasing perfusion of the myocardium and relieving vasospastic angina
  - Relax the veins (vasodilation) reducing the preload and myocardial oxygen consumption
  - Nitroglycerin relaxes vascular smooth muscle by intracellular conversion to nitric oxide which activates quanylate cyclase and increases cells cGMP this leads to dephosphorylation of myosin light chain causing vascular smooth muscle relaxation

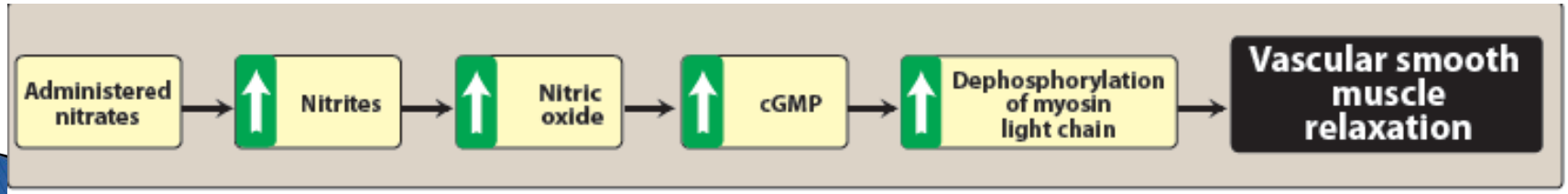


Figure 18.2
Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3', 5'-monophosphate.

Organic nitrates

- For an angina attack caused by exercise or emotional stress sublingual or spray nitroglycerin is the drug of choice

- Nitroglycerin effects
  - Causes dilation of large veins resulting in pooling of blood in veins which decreases preload (venous return) and reduces the work of the heart, decreasing the myocardial oxygen demand
  - Nitroglycerin dilates coronary vasculature, increasing blood supply to the heart muscle

Organic nitrates

- Nitroglycerin is destroyed by first pass effect and so is given sublingually, as spray or patches, the onset of action is in 1 minute

- Isosorbide dinitrate and isosorbide mononitrate are administered orally

Organic nitrates

- Adverse effects
  - Headache
  - High dose can cause postural hypotension, facial flushing, and tachycardia

- Tolerance to the actions of nitrates develops rapidly
  - Blood vessels become desensetized to vasodilation
  - Tolerance can be overcome by providing a daily nitrate free interval, usually 10-12 hours at night, to restore drug sensitivity
  - Nitroglycerin patches are worn for 12 hours then removed for 12 hours
  - Variant angina worsens in the morning, so the nitrate free interval should be in the afternoon

β-Blockers

- β adrenergic blockers decrease the oxygen demand of the myocardium by lowering the rate and force of contraction of the heart
- β-Blockers suppress the activation of the heart by blocking β1 receptors
- They reduce the work of the heart by decreasing heart rate, contractility, cardiac output and blood pressure
- The demand for oxygen by the myocardium is reduced during exertion or rest
- β-Blockers are the drug of choice for effort induced angina
- They reduce the frequency and severity of angina attacks

β-Blockers

- Atenolol (β1 blocker)
- Metoprolol (β1-blocker)
- Propranolol (non-cardio selective, contraindicated in asthma)
- Selective β1-blockers are preferred
- β-Blockers can be used with nitrates to increase exercise duration and tolerance in patients with classic angina (effort induced angina)
- β-Blockers are contraindicated in patients with asthma, severe bradycardia, chronic obstructive pulmonary disease and diabetes
- They should not be discontinued abruptly, to avoid rebound angina, myocardial infarction and hypertension

Calcium channel blockers

- Nifedipine
- Verapamil
- Diltiazem

Calcium channel blockers

- Calcium is essential for muscular contraction
- Calcium influx is increased in ischemia because hypoxia produces membrane depolarization
- This promotes the activity of several ATP consuming enzymes depleting energy stores and worsening the ischemia

Calcium channel blockers

- Calcium channel blockers protect the tissue by inhibiting calcium entry into cardiac and smooth muscle cells of coronary and systemic arteries
- Cause vasodilation, reducing smooth muscle tone and vascular resistance and decrease blood pressure
- They decrease the myocardium oxygen consumption by reducing afterload
- They may worsen heart failure due to their negative inotropic effect

Calcium channel blockers

- Can be used for treatment of effort induced angina due to the reduction in myocardial oxygen consumption because of the decreased afterload
- Can be used for vasospastic angina because of the relaxation of coronary arteries
- Variant angina caused by spontaneous coronary spasm either at work or at rest, rather than increased myocardial oxygen demand is treated by organic nitrates or calcium channel blockers, β-blockers are contraindicated
- Verapamil mainly affects the myocardium while nifedipine mainly affects the smooth muscle in the peripheral vasculature, diltiazem is intermediate in its actions

Nifedipine

- Dihydropyridine derivative
- Arteriolar vasodilator
- Has minimal effect on cardiac conduction or heart rate
- Used for treatment of variant angina caused by spontaneous coronary vasospasm
- Adverse effects
  - Hypotension
  - Flushing
  - Headache
  - Constipation
  - Can cause reflex tachycardia if peripheral vasodilation is marked

Verapamil

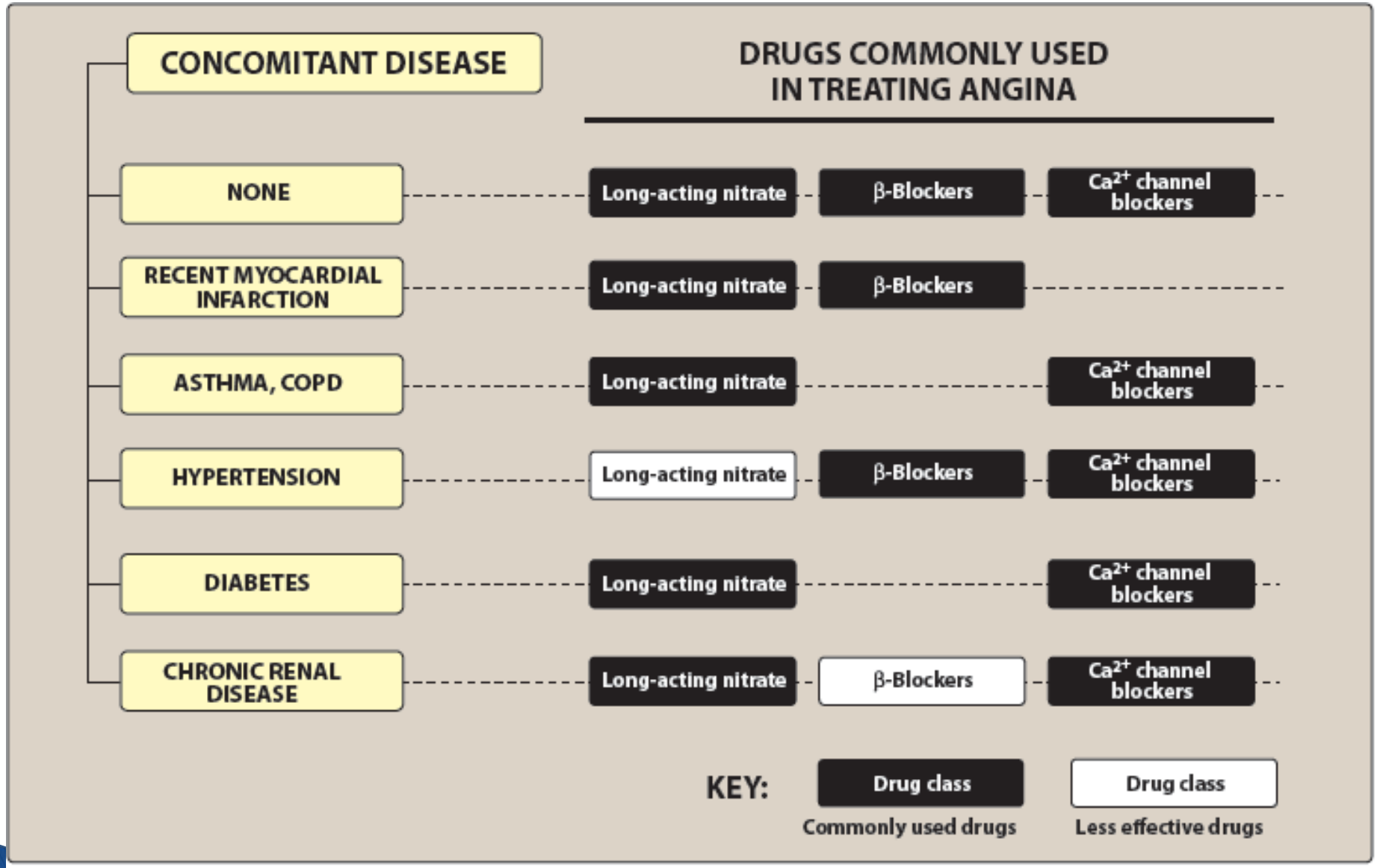
- Diphenylalkylamine
- Slows cardiac atrioventricular conduction
- Decreases heart rate, contractility, blood pressure and oxygen demand
- Causes greater negative inotropic effect than verapamil and is a weaker vasodilator
- Contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities
- Verapamil increases digoxin levels, should be used carefully in patients taking digoxin
- Adverse effects: constipation

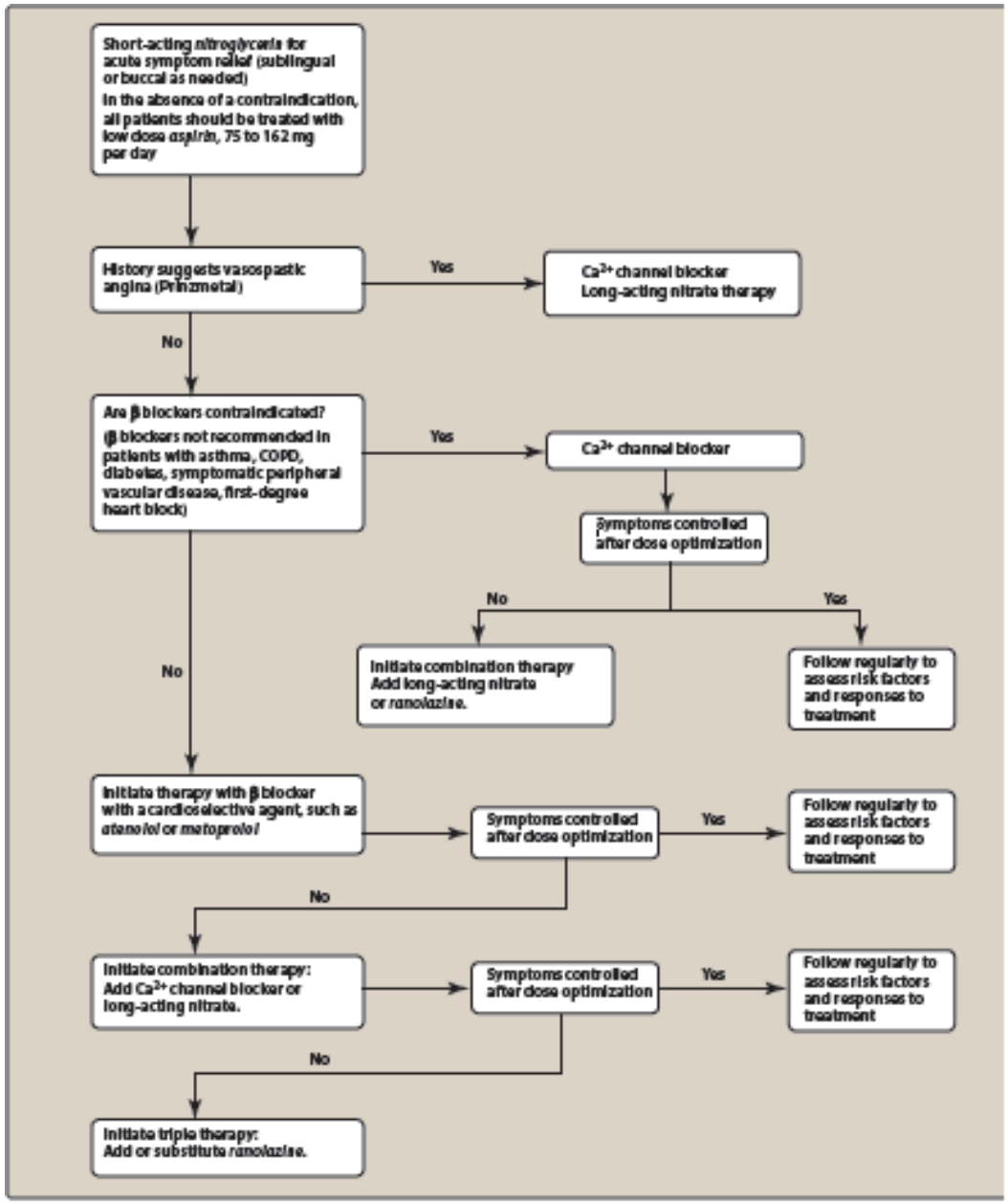
Diltiazem

- Slows AV conduction and decrease the rate of firing of SA node
- Reduces heart rate and blood pressure
- Can relieve coronary artery spasm and so can be used for variant angina
- Adverse effects: constipation

Sodium channel blocker

- Ranolazine
- Inhibits late phase of the sodium current improving oxygen supply and demand equation
- Reduces intracellular sodium and calcium overload, improving diastolic function
- Used for treatment of chronic angina when other treatments fail
- Can be used alone or in combination with other drugs
- Not used for acute angina attacks


CONCOMITANT DISEASE
DRUGS COMMONLY USED IN TREATING ANGINA
NONE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
RECENT MYOCARDIAL INFARCTION
Long-acting nitrate
β-Blockers
ASTHMA, COPD
Long-acting nitrate
Ca2+ channel blockers
HYPERTENSION
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
DIABETES
Long-acting nitrate
Ca2+ channel blockers
CHRONIC RENAL DISEASE
Long-acting nitrate
β-Blockers
Ca2+ channel blockers
KEY:
Drug class
Commonly used drugs
Drug class
Less effective drugs


Short-acting nitroglycerin for acute symptom relief (sublingual or buccal as needed)
In the absence of a contraindication, all patients should be treated with low dose aspirin, 75 to 162 mg per day
History suggests vasospastic angina (Prinzmetal)
Yes
Ca2+ channel blocker
Long-acting nitrate therapy
No
Are β blockers contraindicated?
(β blockers not recommended in patients with asthma, COPD, diabetes, symptomatic peripheral vascular disease, first-degree heart block)
Yes
Ca2+ channel blocker
Symptoms controlled after dose optimization
No
Yes
Initiate combination therapy
Add long-acting nitrate
or ranolazine.
Follow regularly to assess risk factors and responses to treatment
No
Initiate therapy with β blocker with a cardioselective agent, such as atenolol or metoprolol
Symptoms controlled after dose optimization
Yes
Follow regularly to assess risk factors and responses to treatment
No
Initiate combination therapy:
Add Ca2+ channel blocker or long-acting nitrate.
Symptoms controlled after dose optimization
Yes
Follow regularly to assess risk factors and responses to treatment
No
Initiate triple therapy:
Add or substitute ranolazine.