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

Arrhythmias

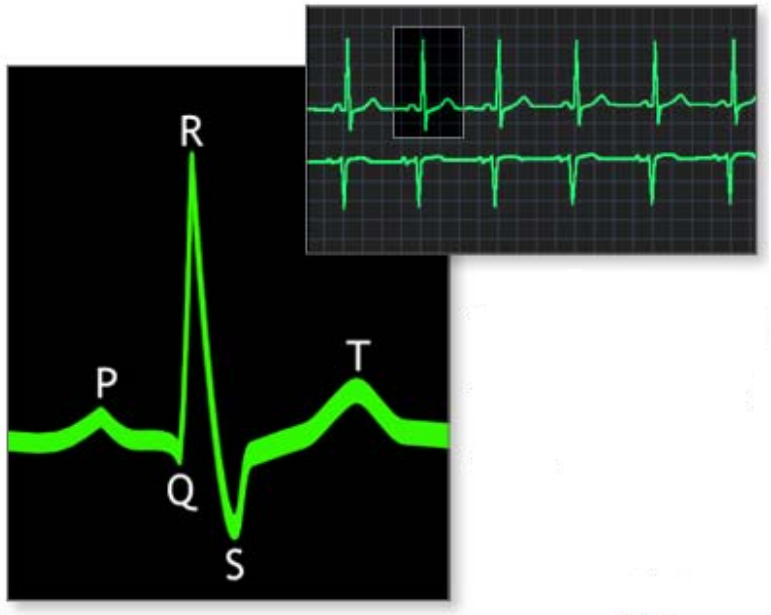
- Abnormalities in impulse formation and conduction in the myocardium
- They are presented with various symptoms
  - Bradycardia (slow heart rate) or tachycardia (rapid heart rate)
  - Heart could be beating regularly (sinus bradycardia, or sinus tachycardia) or irregularly (atrial fibrillation)
- The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

Arrhythmias

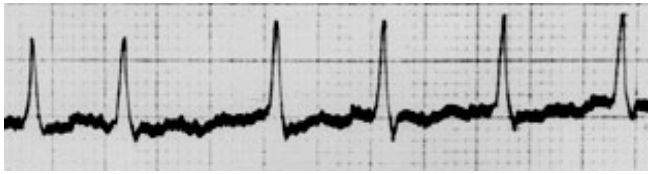
- Types of arrhythmias
  - Atrial arrhytmias
    - Atrial flutter
    - Atrial fibrillation
  - Supraventricular tachycardias
    - AV node reentry
    - Acute suraventricular tachycardia
  - Ventricular tachycardias
    - Acute ventricular tachycardia
    - Ventricular fibrillation

Normal Sinus Rhythm:

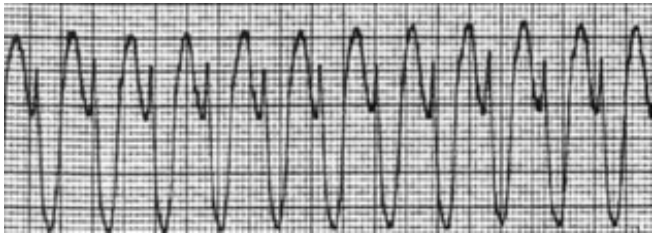
- P wave: Atrial depolarization
- QRS complex: Ventricular depolarization
- T wave: Ventricular repolarization



Abnormal Heart Rhythms



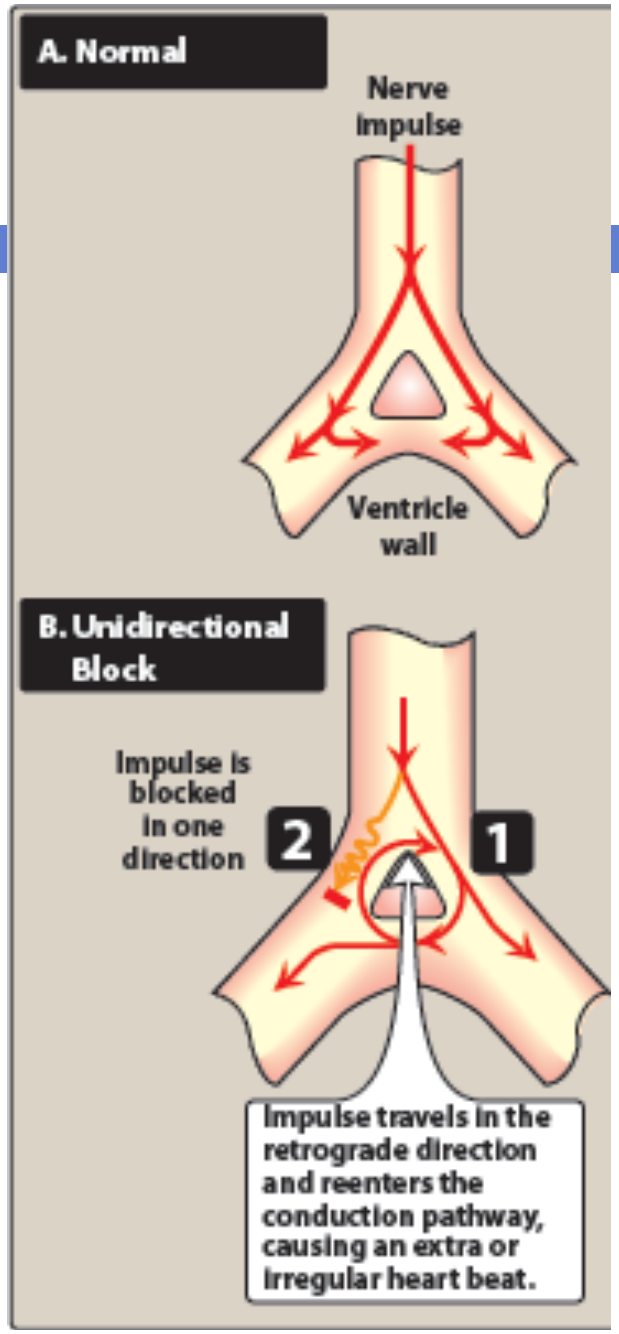
Atrial Fibrillation



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

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

Class I antiarrhythmic drugs

- Block sodium channels and slow the rise of phase 0 of the action potential
- Decrease excitabitliy and conduction velocity
- Quinidine IA (Can cause cinchinism as a side effect: blurred vision, tinnitus, headache, disorientation, and psychosis)
- Procainamide IA
- Lidocaine IB (Drug of choice for emergency ventricular arrhythmias)
- Propafenone IC (Can cause bronchospasm)
- Adverse effects: these drugs can be proarrhythmic (can cause arrhythmia)
- Their use is decreasing

Class II antiarrhythmic drugs

- β- adrenergic antagonists
- Propranolol (Prevention of arrhythmia after MI)
- Metoprolol
- Acebutolol
- Esmolol (short acting, used for acute arrhythmias)
- Antagonize sympathetic nerve activity, decrease heart rate and contractility, decrease SA automaticity, and prolong AV conduction.
- Useful for
  - Tachyarrhythmias
  - Atrial flutter and fibrillation
  - AV nodal reentrant tachycardia

Class III antiarrhythmic drugs

- Block K^+ channels
- Prolong the duration of action potential
- Amiodarone
  - Has Class I, II, III, and IV activity
  - Antiarrhythmic and antianginal
  - Most commonly used antiarrhythmic
  - Used for severe refractory supraventricular and ventricular tachyarrhythmias
  - Used for atrial fibrillation
  - Adverse effects
    - Pulmonary fibrosis
    - Liver toxicity
    - Thyroid dysfunction
- Dronedarone is amiodarone derivative (No thyroid dysfunction)

Class III antiarrhythmic drugs

- Block K^+ channels
- Prolong the duration of action potential
- Sotalol
  - Also has potent non selective β–blocker activity
  - Used for long term therapy to decrease the rate of sudden death following acute MI
  - Used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias.
  - Since sotalol has β -blocking properties, it is commonly used for these indications in patients with left ventricular hypertrophy or atherosclerotic heart disease.
  - Adverse effects
    - Prolongation of QT interval (torsade de pointes) in 4% of patients

Class IV antiarrhythmic drugs

- Calcium channel blockers
- Slow the conduction in tissues that depend on Ca currents (AV node)
- Verapamil
- Diltiazem
- Used for hypertension, angina and arrhythmia
- More effective against atrial than ventricular arrhythmias
- Contraindicated in patients with depressed cardiac function, they have negative inotropic effect

Other antiarrhythmic drugs

- Digoxin
  - Used for atrial fibrillation and flutter
  - At toxic doses can cause ventricular tachycardia and fibrillation

- Adenosine
  - Decreases conduction velocity and automaticity in the AV node
  - Short duration of action (15 seconds)
  - IV adenosine is used for acute supraventricular tachycardia

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

- Patients with atrial fibrillation/ atrial flutter should be started on anticoagulant therapy
- Patients who have been in atrial fibrillation *may have formed thrombus.*
  - This predisposes the patient to embolic events such *as myocardial infarctions, infarctions of organ systems - i.e. - strokes.*

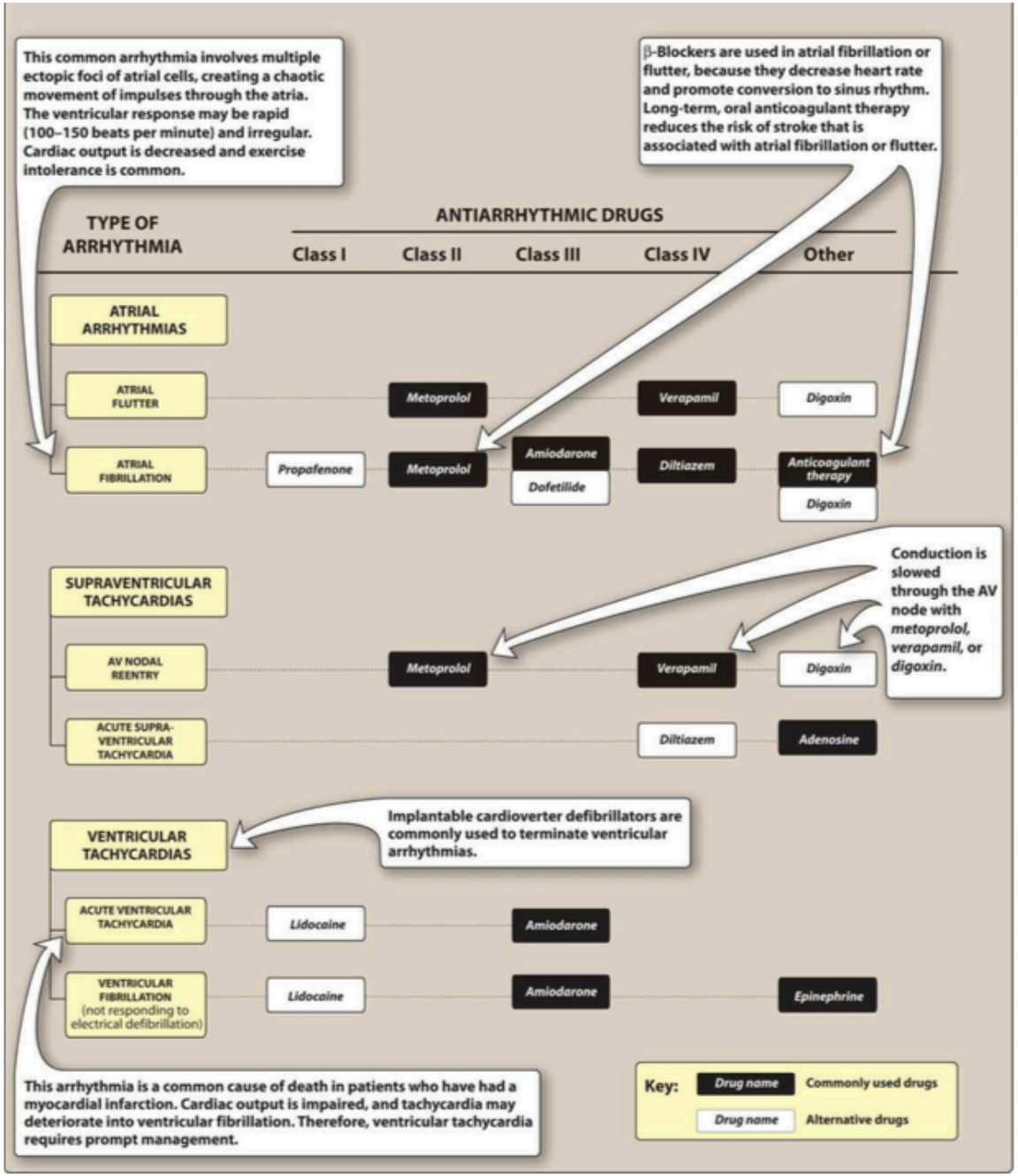
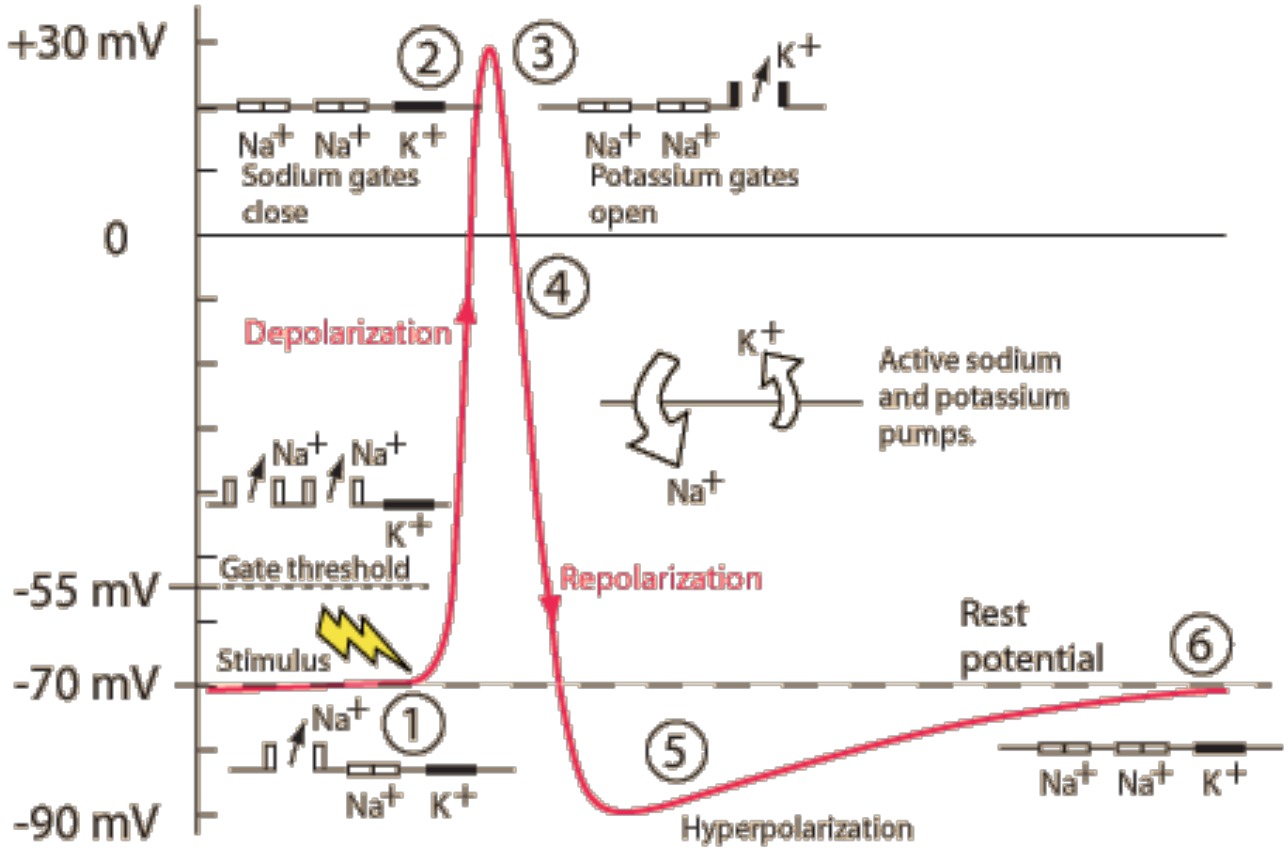


Figure 19.2 Therapeutic indications for some commonly encountered arrhythmias. AV = atrioventricular.


+30 mV
0
-55 mV
-70 mV
-90 mV
2
3
Na+ Na+ K+
Sodium gates close
Na+ Na+
K+
Potassium gates open
4
Depolarization
K+
Active sodium and potassium pumps.
Na+
Na+ Na+
K+
Gate threshold
Repolarization
Rest potential
6
Stimulus
Na+
1
Na+ K+
5
Hyperpolarization
Na+ Na+ K+

ANTIHYPERLIPIDEMIC DRUGS

- Coronary artery disease is a leading cause of death

- Coronary artery disease is correlated with:
  - High levels of LDL cholesterol and triglycerides
  - Low levels of HDL cholesterol
  - Smoking
  - Hypertension
  - Obesity
  - Diabetes

- Hyperlipidemias can be due to lifestyle like lack of exercise or excess saturated fatty acid diet or from genetic factors

- Antihyperlipidemic drugs should be taken indefinitely, because if therapy is terminated plasma lipid levels return to pretreatment levels

Serum levels

- Total cholesterol
  - Desirable values <200 mg/dL or <5.2 mmol/L
  - High >240 mg/dL or >6.2 mmol/L

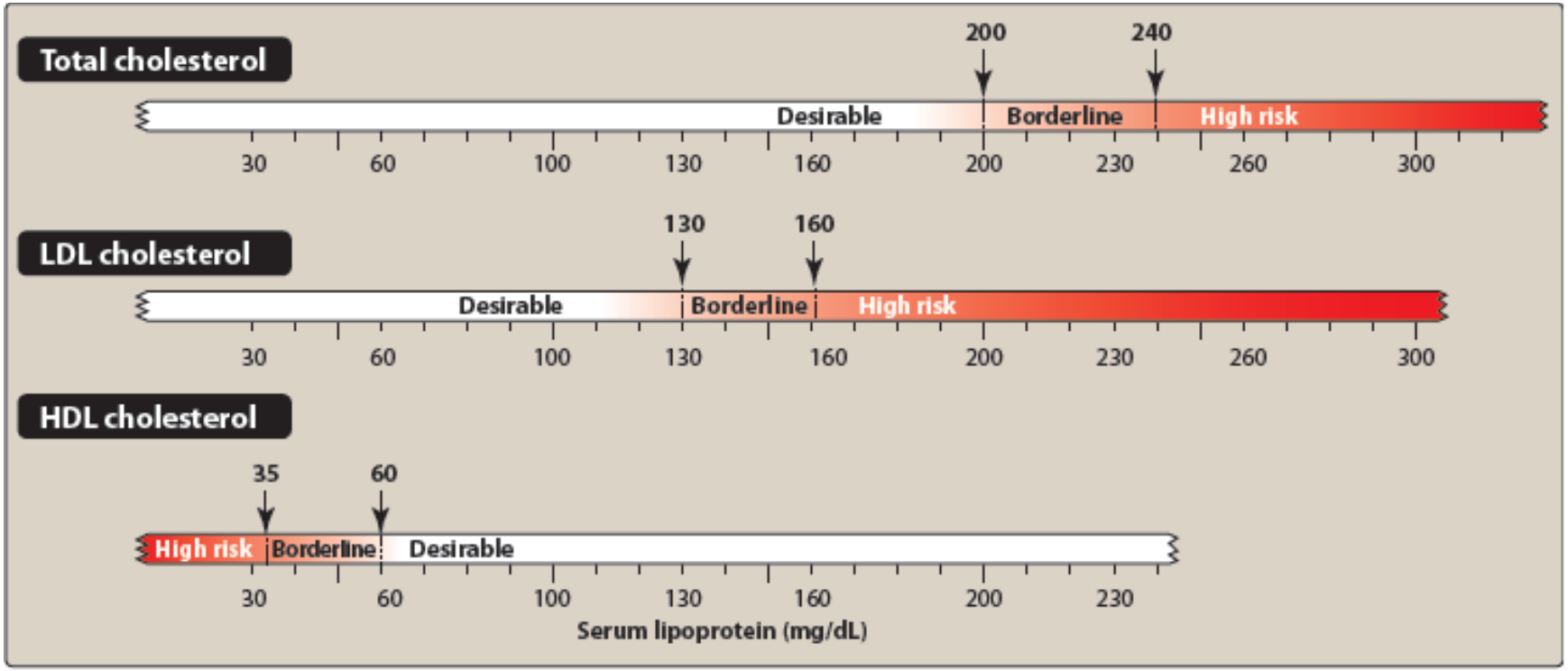
- LDL cholesterol
  - Ideal <100 mg/dL or <2.6 mmol/L

  (<70 mg/dL or<1.8 mmol/L for people at very high risk of heart disease)
  - High >160 mg/dL or >4.1 mmol/L

Serum levels

- Triglycerides
  - Desirable <150 mg/dL or <1.7 mmol/L
  - High >200 mg/dL or >2.3 mmol/L

- HDL
  - Best >60 mg/dL or >1.6 mmol/L
  - Poor <40 mg/dL or <1 mmol/L (Men)
  - Poor <50 mg/dL or <1.3 mmol/L (Women)


Total cholesterol
200
240
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
LDL cholesterol
130
160
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
HDL cholesterol
35
60
High risk
Borderline
Desirable
30
60
100
130
160
200
230
Serum lipoprotein (mg/dL)

Hyperlipidemias

- Primary treatment goal of hyperlipidemias:
  - Reduction of LDL

- Treatment options of hypercholesterolemia
  - Lifestyle changes: diet, exercise, weight reduction can decrease LDL and increase HDL
  - Patients usually do not modify their lifestyle enough to lower LDL and then pharmacological agents need to be added

Antihyperlipidemic drugs

- Used for elevated serum lipids
- Mechanism of action could be one of these:
  - Decrease production of lipoproteins carriers of cholesterol and triglycerides
  - Increase degradation of lipoprotein
  - Decrease cholesterol synthesis
  - Decrease cholesterol absorption
  - Increase cholesterol removal from the body
- Should be accompanied by low dietary intake of saturated and trans fat and close monitoring of caloric intake

Antihyperlipidemic drugs

- HMG CoA reductase inhibitors
- Niacin
- Fibrates
- Bile binding resins
- Cholesterol absorption inhibitor

HMG CoA reductase inhibitors

- Commonly known as statins
- Include
  - Simvastatin
  - Lovastatin
  - Pravastatin
  - Atorvastatin
  - Rosuvastatin
  - Fluvastatin

HMG CoA reductase inhibitors

- Mechanism of action
  - Inhibit the enzyme involved in the first step of cholesterol synthesis 3-hydroxy-3-methylglutaryl conenzyme A (HMG CoA), causing depletion of intracellular cholesterol
- Lower LDL
- First line treatment for patients with high LDL cholesterol

HMG CoA reductase inhibitors

- Adverse effects
  - Abnormalities in liver function
  - Myopathy and rhabdomyolysis (disintegration of muscle). Rare

- Contraindicated in Pregnancy, nursing mothers

Antihyperlipidemics

- Niacin
  - Inhibits lipolysis in adipose tissue, decreasing free circulating fatty acids
- Fibrates
  - Fenofibrate
  - Decrease triglyceride concentration by increasing lipoprotein lipase which breaks down triacylglyecrol

Antihyperlipidemics

- Bile acid binding resins
  - Cholestyramine
  - Bind to bile acids and bile salts in the small intestine forming a complex that gets excreted, this causes increased conversion of cholesterol into bile acids
- Cholesterol absorption inhibitor
  - Ezetimible
  - Inhibits absorption of cholesterol in the small intestine