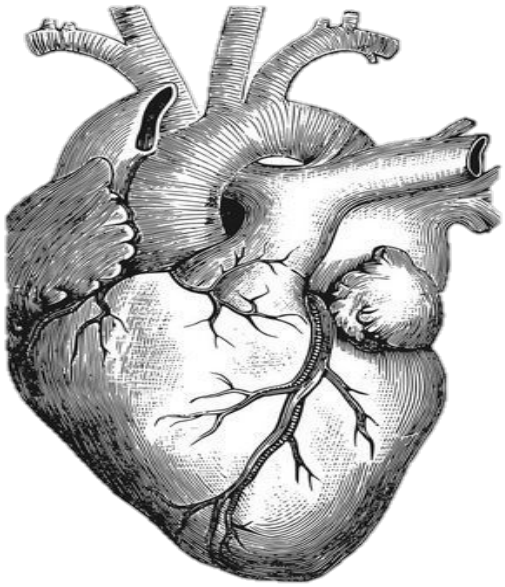
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



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Antiarrhythmic Drugs

Objectives:

- Understand definition of arrhythmias and their different types.
- Describe different classes of Antiarrhythmic drugs and their mechanism of action.
- Understand their pharmacological actions, clinical uses, adverse effects and their interactions with other drugs.

Important Notes Extra

Review

	Sympathetic		Parasympathetic	
Organ	Action	Receptor	Action	Receptor
Heart				
SA node, heart rate	↑	β_1	↓	M
AV nodal conduction	↑	β_1	↓	M
Contractility	↑	β_1	↓ (atria only)	M
Vascular Smooth Muscle				
Skin; splanchnic	Constricts	α_1		
Skeletal muscle	Dilates	β_2		
Skeletal muscle	Constricts	α_1		
Endothelium			Releases EDRF	M
Bronchioles	Dilates	β_2	Constricts	M
Gastrointestinal Tract				
Smooth muscle, walls	Relaxes	α_2, β_2	Contracts	M
Smooth muscle, sphincters	Contracts	α_1	Relaxes	M
Saliva secretion	↑	β_1	↑	M
Gastric acid secretion			↑	M
Pancreatic secretion			↑	M
Bladder				
Wall, detrusor muscle	Relaxes	β_2	Contracts	M
Sphincter	Contracts	α_1	Relaxes	M
Male Genitalia	Ejaculation	α	Erection	M
Eye				
Radial muscle, iris	Dilates pupil (mydriasis)	α_1		
Circular sphincter muscle, iris			Constricts pupil (miosis)	M
Ciliary muscle	Dilates (far vision)	β	Contracts (near vision)	M
Skin				
Sweat glands, thermoregulatory	↑	M*		
Sweat glands, stress	↑	α		
Pilomotor muscle (goose bumps)	Contracts	α		
Lacrimal Glands			Secretion	M
Liver	Gluconeogenesis; glycogenolysis	α, β_2		
Adipose Tissue	Lipolysis	β_1		
Kidney	Renin secretion	β_1		

AV, Atrioventricular; EDRF, endothelial-derived relaxing factor; M, muscarinic receptor; SA, sinoatrial.
*Sympathetic cholinergic neurons.

What is Arrhythmia?

- It is a pathologic condition in which the heart's rhythm is abnormal;

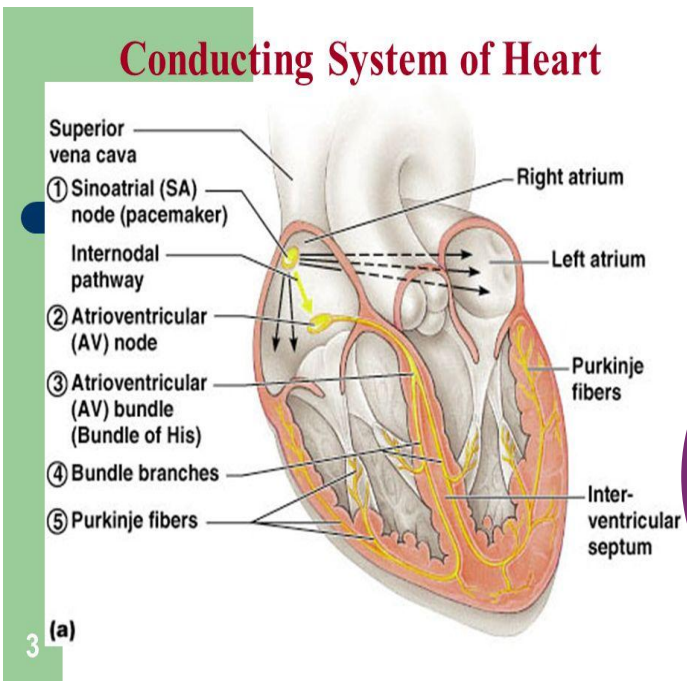
1	Rate	• **>100 Tachycardia** • **<60 Bradycardia**
2	Regularity	• **Extrasystoles (PAC, PVC)** • **Extrasystole is a premature contraction of the heart that is independent of the normal rhythm.**
3	Site of Origin	• **Ectopic pacemakers or disturbance in conduction.** • **Ectopic : Ectopic foci are abnormal pacemaker (outside of the SA node that display automaticity. Their activity is normally suppressed by the higher rate of the SA node. An excitable group of cells that causes a premature heart beat.**
4	Disturbance in Conduction	• **Conduction is the progression of electrical impulses through the heart which cause the heart to beat. AV node is usually responsible for this.**

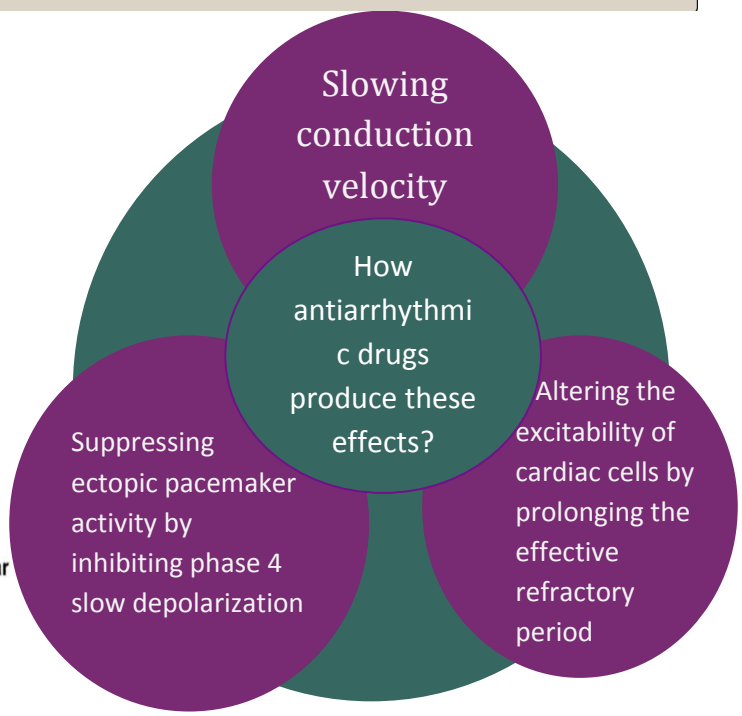
The ultimate goal of therapy is to restore normal rhythm & conduction by:

- **Prevention** of more serious arrhythmias
- Maintenance of normal rhythm

Vaughn-Williams Classification of Antiarrhythmic Drugs:

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





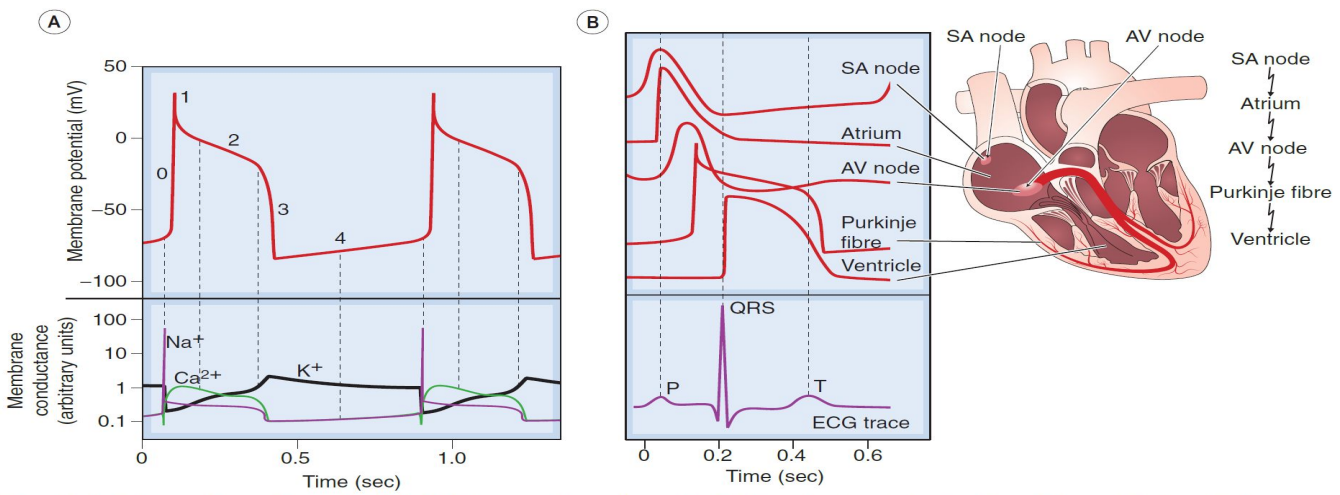


Fig. 21.1 The cardiac action potential. [**A**] Phases of the action potential: 0, rapid depolarisation; 1, partial repolarisation; 2, plateau; 3, repolarisation; 4, pacemaker depolarisation. The lower panel shows the accompanying changes in membrane conductance for Na^+, K^+ and Ca^{2+}. [**B**] Conduction of the impulse through the heart, with the corresponding electrocardiogram (ECG) trace. Note that the longest delay occurs at the atrioventricular (AV) node, where the action potential has a characteristically slow waveform. SA, sinoatrial.

Class I:

1- Decrease the rate of rise of rapid depolarization (Phase 0)

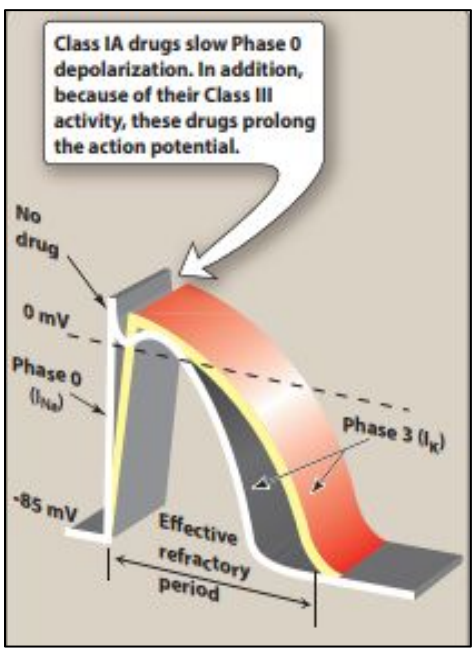
Drugs that block the influx of Na ions through Na channels (membrane stabilizing effect). Either partial or complete block.

2- Decrease phase 4 slow diastolic depolarization (suppress pacemaker activity).

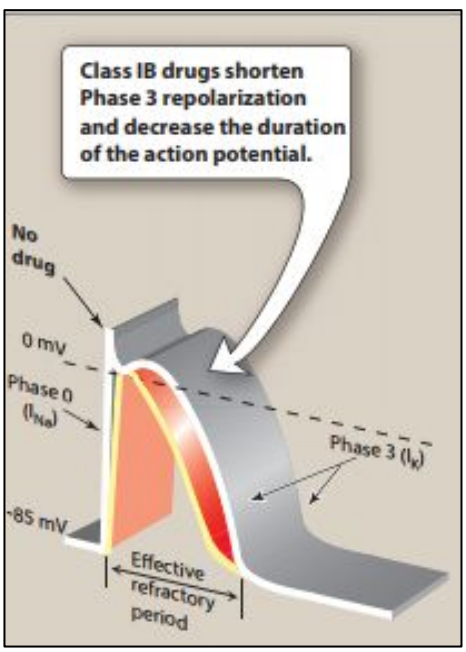
It is very important to know the mechanism of action of each class and subclass.

- Subclassified according to their effect on action potential duration (phase 3):

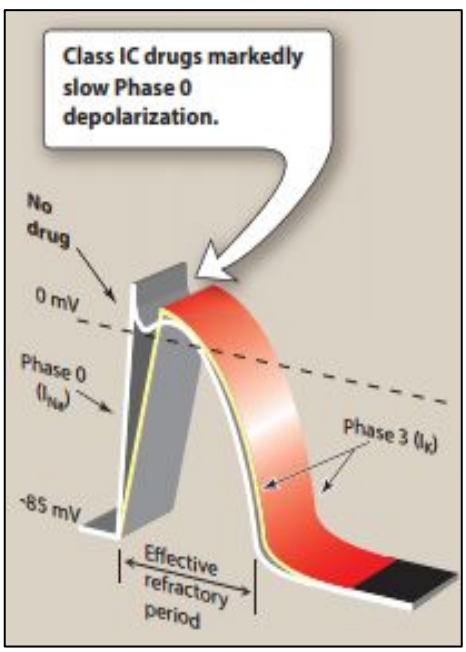
IA: prolongs action potential duration:



IB: shorten action potential duration:



IC: no effect on action potential duration:



Class IA (Na Channel Blockers)

Drug	Quinidine		Procainamide
Pharmacological action	Cardiac effects (direct): 1. Membrane stabilizing effect. 2. ECG changes: ❖ Prolongs P-R and Q-T interval. ❖ Widens QRS complex.	Actions on ANS (indirect): 1. Anticholinergic (atropine like) effect: ❖ Increase conduction through the A.V. node (risk of ventricular tachycardia). 2. α-adrenergic blocking effect: ❖ Causes vasodilatation & reflex sinus tachycardia (seen more after I.V dose).	Similar to Quinidine except: 1. Less toxic on the heart. 2. There is no anticholinergic or α-blocking actions. This is why it is less toxic on the heart.
Clinical use	1. Atrial flutter & fibrillation. 2. Maintaining sinus rhythm after cardioversion (conversion from arrhythmia to a normal rhythm using electricity or drugs) 3. Is also an Anti-malaria drug		❖ More effective in ventricular than in atrial arrhythmias
ADRs	1. Quinidine syncope: episodes of fainting due to Torsades de pointes arrhythmia. (it's in therapeutic dose) 2. Anticholinergic adverse effects: Dry mouth - Blurred vision - Urinary retention – Constipation. 3. Hypotension - due to depressing contractility(-ve inotropic effect) & vasodilatation.		1. In long term therapy causes reversible lupus erythematosus-like syndrome (SLE). 2. Hypotension. 3. Torsades de pointes arrhythmia in toxic doses 4. Hallucination & psychosis in long term use
Administration	Given orally (rarely given I.V.) Why? to minimize side effects.		I.V. (used in emergency)

Class IB (Na Channel Blockers)

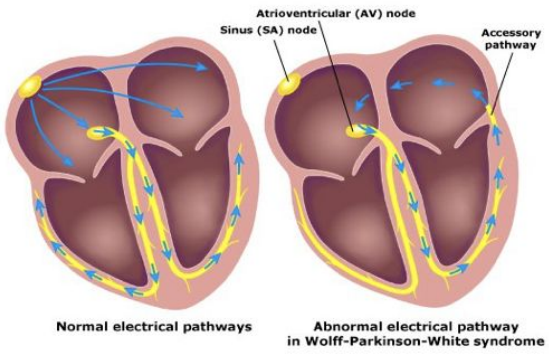
Drug	Lidocaine	Mexiletine
Pharmacological actions:	❖ In addition to sodium channel blockade, lidocaine and mexiletine shorten phase 3 repolarization and decrease the duration of the action potential.	
Therapeutic uses:	1. During surgery. 2. Following acute myocardial infarction. 3. treatment of emergency ventricular arrhythmias	1. Ventricular arrhythmia. 2. Digitalis-induced arrhythmias = arrythmias induced by drugs
Pharmacokinetics:	❖ NOT effective in atrial arrhythmias ❖ NOT effective orally (3% bioavailability) ❖ given I.V. bolus or slow infusion ❖ $t_{1/2}$ = 2 hours (4mg, if it reaches 9 mg it will cause convulsions)	❖ Effective orally ❖ $t_{1/2}$ = 10 hours هذي هي مزايا العلاج هذا
Adverse effects:	1. Hypotension (because of -ve inotropic effect) 2. Similar to other local anesthetics,causes CNS adverse effects such as: 3. Paresthesia 4. Tremor 5. Dysarthria (slurred speech) 6. Tinnitus 7. Confusion 8. Convulsions (هذي الأعراض اذا ظهرت عند المريض لازم توقف العلاج عشان ما توصل ل convulsions)	1. Nausea 2. Vomiting 3. Tremor 4. Drowsiness, 5. Diplopia 6. Arrhythmias 7. Hypotension

Class IC (Na Channel Blockers)

Drug	**Flecainide**
Pharmacological actions:	❖ Has no effect on action potential duration, suppresses phase 0 upstroke in Purkinje and myocardial fibers. This causes marked slowing of conduction in all cardiac tissue.
Therapeutic uses:	❖ Supraventricular arrhythmias. i.e atrial arrythmias ❖ Wolff-Parkinson-White syndrome*. ❖ Very effective in ventricular arrhythmias, but very high risk of proarrhythmia. ❖ Should be reserved for resistant arrhythmias. (We use this drug, if the arrhythmia is resistance to drugs)
Adverse effects:	1. Proarrhythmia 2. CNS: dizziness, tremor, blurred vision, abnormal taste sensations, paraesthesia 3. Heart failure due to -ve inotropic* effect. *Inotropic: modifying the force or speed of contraction of muscles.

Wolff-Parkinson-White syndrome (WPW):

❖ It is the Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent. (it is a re-entry arrhythmia, where the electrical signal re-enters the AV node)



Class II (β- adrenoceptor blockers)

Pharmacological actions:

- ❖ Block β_1- receptors in the heart
- ❖ Reduce the sympathetic effect on the heart
  - ➢ This decreases the automaticity of the S.A. node & ectopic pacemakers
  - ➢ It also prolongs the refractory period (slows the conduction speed) of the A.V. node.

Therapeutic uses:

1. Atrial arrhythmias associated with emotion (After exercise/ Thyrotoxicosis *Hyperthyroidism*)
2. Wolff-Parkinson-White syndrome (WPW)
3. Digitalis *(Digoxin toxicity)* induced arrhythmias

Esmolol	**Propranolol, Atenolol, Metoprolol:**
❖ Given IV for rapid control of ventricular rate in patients with atrial flutter or fibrillation.	❖ Are used in patients with myocardial infarction to reduce the incidence of sudden death due to ventricular arrhythmias.

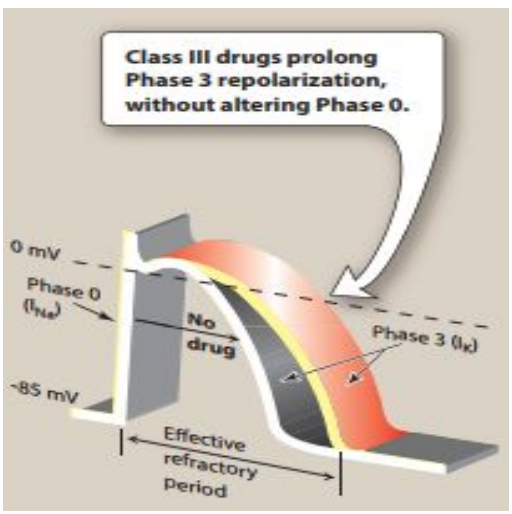
Pharmacokinetics:

- ❖ Very short acting (Half life = 9 mins)

Class III Drugs

AMIODARONE

Prolong phase 3 repolarization



Class III

Drug	Amiodarone
Pharmacological actions:	1. Prolongs the action potential duration, thus prolongs refractory period main effect it will partially block the K+efflux which will prolong the phase 3 duration 2. Contains additional Class Ia, II, & IV effects 3. Vasodilation 4. Calcium channel block; due to α- & β-adrenoceptor blocking effects.
Therapeutic uses:	❖ Main use: serious resistant ventricular arrhythmias. ❖ Maintenance of sinus rhythm after cardioversion. ❖ Resistant supraventricular arrhythmias e.g. WPW
ADRs:	1. Exacerbation of ventricular arrhythmias (if high dose) 2. Bradycardia & heart failure 3. Pulmonary fibrosis occurs in 15% of cases 4. Hyper/Hypothyroidism this is due to the iodine in the drug 5. Photodermatitis & skin deposits (patients should avoid exposure to sunlight) 6. Neurological side effects: tremors & peripheral neuropathy 7. Nausea, vomiting & constipation 8. Corneal micro deposits 9. Hepatocellular necrosis
Pharmacokinetics:	❖ Metabolized by CYP3A4 & CYP2C8 to its major active metabolite: N-desethylamiodarone. ❖ Eliminated primarily by hepatic metabolism. ❖ Cross placenta & appears in breast milk. ❖ Extremely long half life: $t_{1/2}$ = 13 - 103 days.

Drug interactions:	• Co-administration of Amiodarone with drugs that prolong the QT interval increases risk of Torsades de Pointes e.g.
	  ○ Macrolide antibiotics (Clarithromycin, Erythromycin)
	  ○ Azole antifungals (Ketoconazole)
	• Drugs that inhibit enzymes; cause increase in serum concentration of Amiodarone this can cause toxicity e.g.
	  ○ Loratadine, Ritonavir, Trazodone, Cimetidine, Grapefruit juice.
	• Drugs that induce enzymes; cause decrease in serum concentration of Amiodarone e.g.
	  ○ Rifampin

Pure Class III

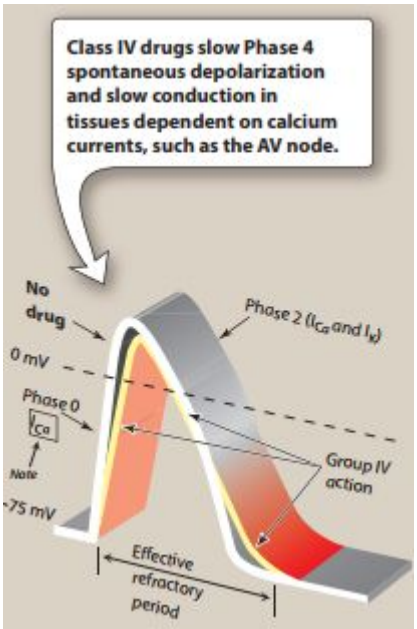
Drug:	Ibutilide
Therapeutic uses:	❖ Used for the acute conversion of atrial flutter or fibrillation to normal sinus rhythm.
Administration:	❖ Given by rapid IV infusion
ADRs:	❖ Causes QT interval prolongation (may cause torsades de pointes)

Class IV

calcium channel blockers

1- Slowing of conduction

2- Prolongation of effective refractory period



Drug	ADENOSINE Other anti arrythmia) (drugs	Class IV (Ca channel blocker)	
		Verapamil	Diltiazem
M.O.A	Inhibits cAMP by binding to adenosine A1 receptors causing the following actions: 1. Opening of potassium channels (hyperpolarization) 2. Decreasing conduction velocity mainly at AV node (negative dromotropic effect) 3. Inhibiting phase 4 pacemaker action potential at SA node (negative chronotropic effect)	Blocking calcium channel main site of action is A.V.N & S.A.N Causes: 1. Slowing of conduction. 2. Prolongation of effective refractory period.	
Therapeutic uses	❖ Drug of choice for acute management of paroxysmal supraventricular tachycardia ❖ Preferred over verapamil (safer and does not depress contractility) ❖ Half-life = less than 10 sec ❖ given via injection	❖ Atrial arrhythmias ❖ Re-entry supraventricular arrhythmias (e.g. WPW) ❖ NOT effective in ventricular arrhythmias	
Adverse effects	❖ Flushing in about 20% of patients ❖ Shortness of breath and chest burning in 10% of patients (due to bronchospasm) ❖ Brief AV block (contraindicated in heart block and ischemia)	_____	

New Antiarrhythmic Drugs

Dronedarone

- A non-iodinated congener of amiodarone
- Has antiarrhythmic properties belonging to all four classes
- Used for maintenance of sinus rhythm following cardioversion in patients with atrial fibrillation

هذا العلاج شالوا منه اليود عشان كذا اغلب الأعراض الجانبية راحت وبالتالي نقدر نستخدمه للمريض اللي يعاني من Hypo/hyperthyroidism

WARNINGS

- Should not be used in patients with severe (class IV) heart failure. Risk of death may be increased in these patients.
- Should not be used in patients with permanent atrial fibrillation. Risk of death and stroke, may be increased in these patients.

Bradyarrhythmias

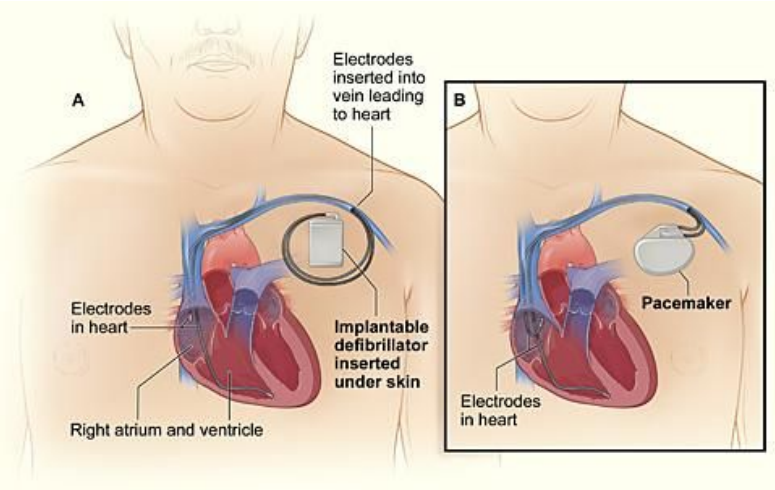
Atropine

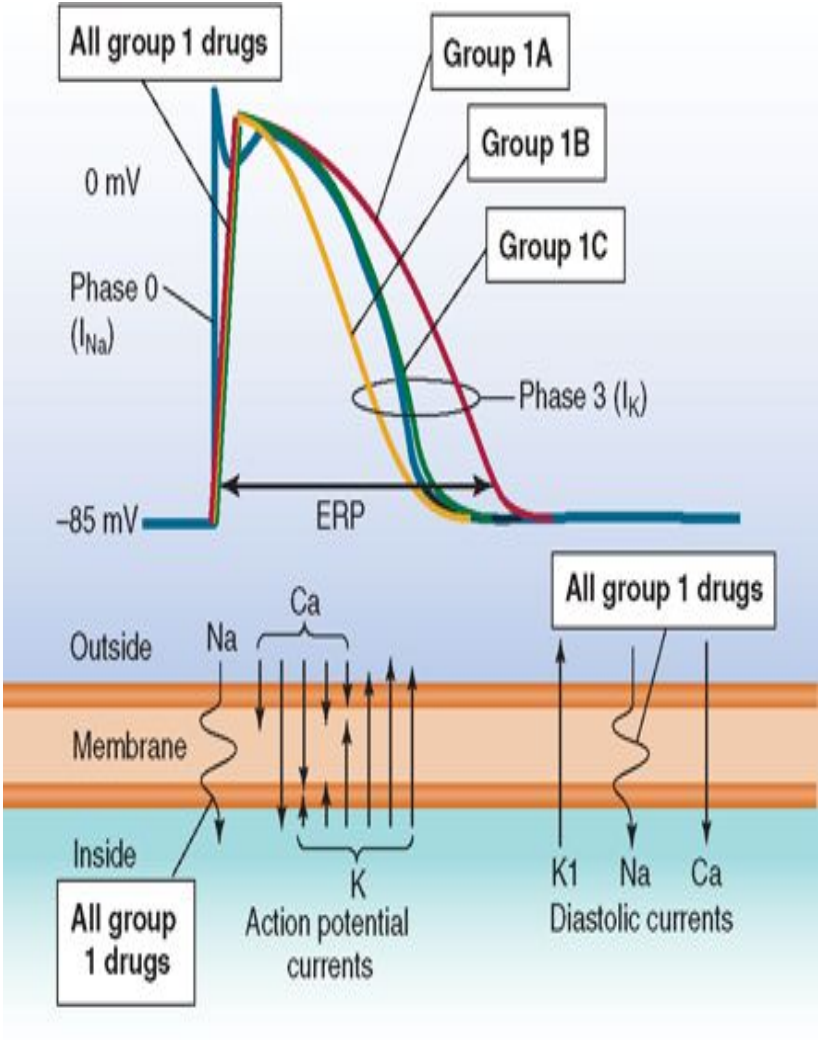
- Used in sinus bradycardia after myocardial infarction and in heart block .
- In emergency heart block isoprenaline may be combined with atropine (caution). The danger with this is risk of tachycardia

NONPHARMACOLOGIC THERAPY OF ARRHYTHMIAS

Implantable Cardiac Defibrillator (ICD)

- Can automatically detect and treat fatal arrhythmias such as ventricular fibrillation





Beta blockers summary:

1- Prevent β-receptor activation, which would normally ↑ cAMP

2- ↓ SA and AV nodal activity

3- ↓ Slope of phase 4 (diastolic currents) of AP in pacemakers

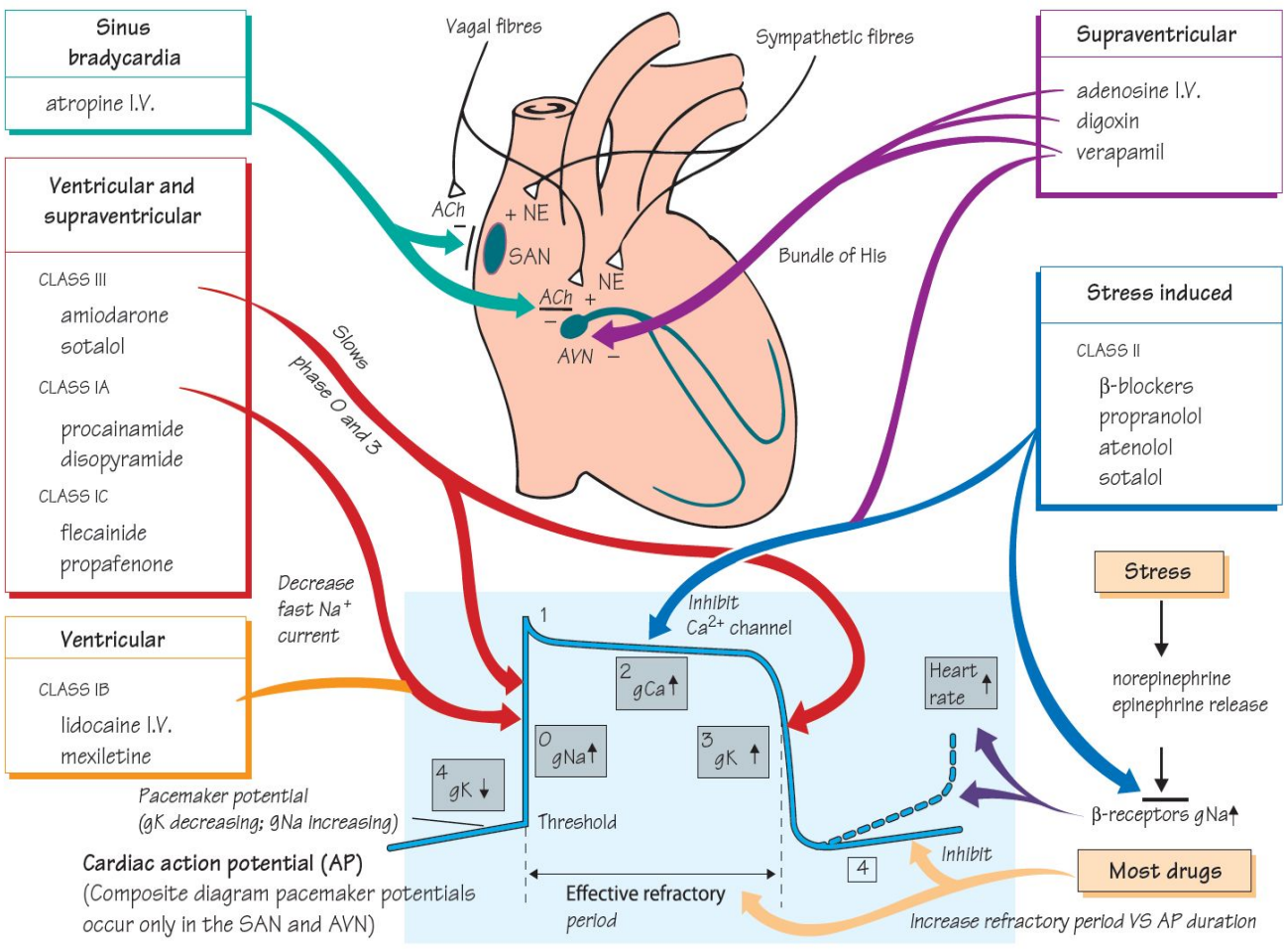
4- Drugs:

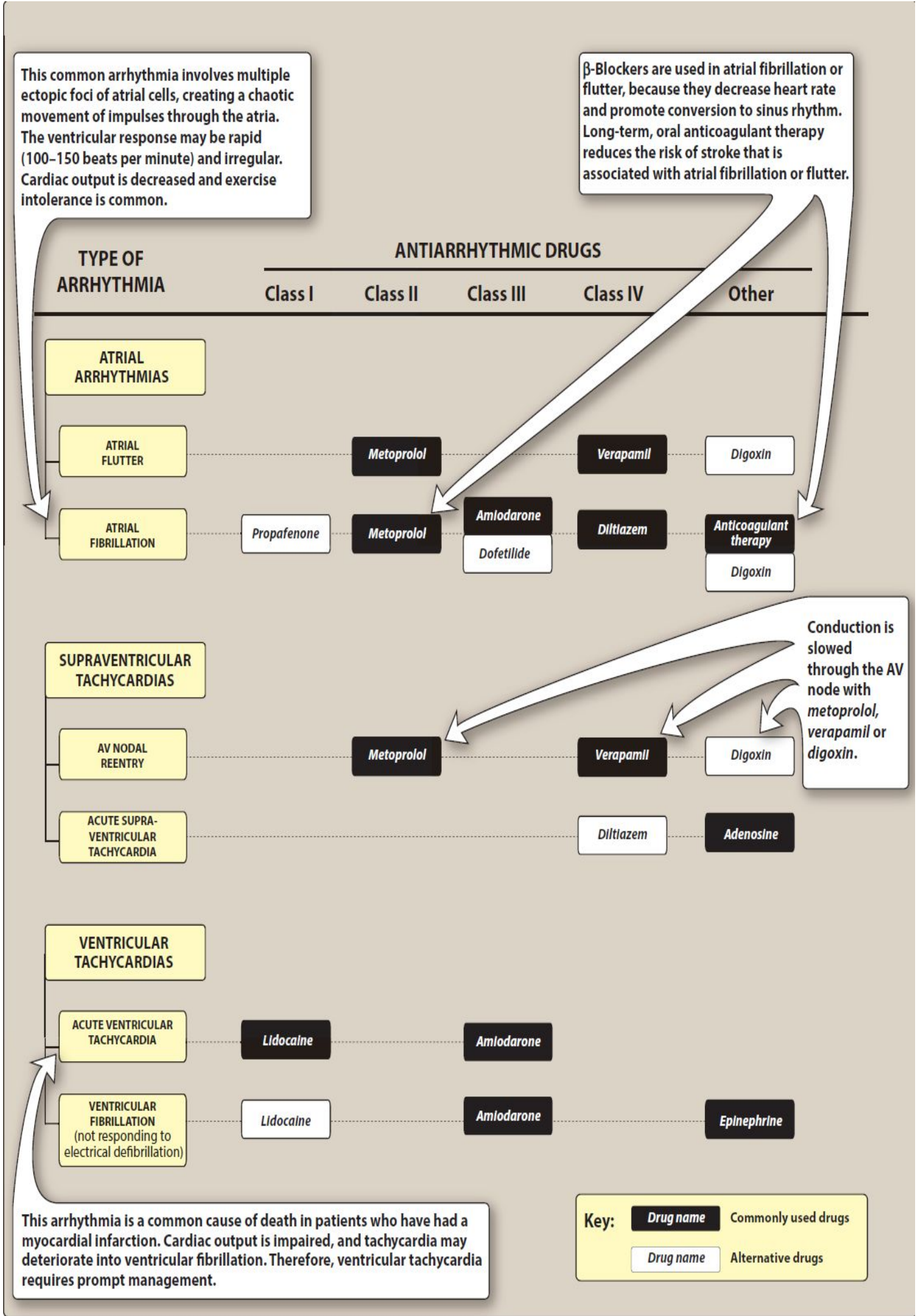
– Propranolol (nonselective) and the cardioselective drugs: acebutolol and esmolol

– Uses:

- Prophylaxis post-MI and in supraventricular tachyarrhythmias (SVTs)
- Esmolol (IV) is used in acute SVTs

Extra images




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
SUPRAVENTRICULAR TACHYCARDIAS
Conduction is slowed through the AV node with metoprolol, verapamil or digoxin.
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

Questions

MCQs:

1. A 57-year-old man is admitted to the emergency department with chest pain and a fast irregular heart rhythm. The ECG shows an inferior myocardial infarction and ventricular tachycardia. Lidocaine is ordered. When used as an antiarrhythmic drug, lidocaine typically

A. Increases action potential duration
B. Increases contractility
C. Increases PR interval
D. Reduces abnormal automaticity

2. A 16-year-old girl has paroxysmal attacks of rapid heart rate with palpitations and shortness of breath. These episodes occasionally terminate spontaneously but often require a visit to the emergency department of the local hospital. Her ECG during these episodes reveals an AV nodal tachycardia. The antiarrhythmic of choice in most cases of acute AV nodal tachycardia is

A. Adenosine
B. Amiodarone
C. Flecainide
D. Verapamil

3. A 60-year-old man comes to the emergency department with severe chest pain. ECG reveals ventricular tachycardia with occasional normal sinus beats, and ST-segment changes suggestive of ischemia. A diagnosis of myocardial infarction is made, and the man is admitted to the cardiac intensive care unit. His arrhythmia should be treated immediately with

A. Adenosine
B. Verapamil
C. Lidocaine
D. Quinidine

4. Which of the following drugs slows conduction through the AV node and has its primary action directly on calcium channels?

A. Mexiletine
B. Flecainide
C. Diltiazem
D. Esmolol

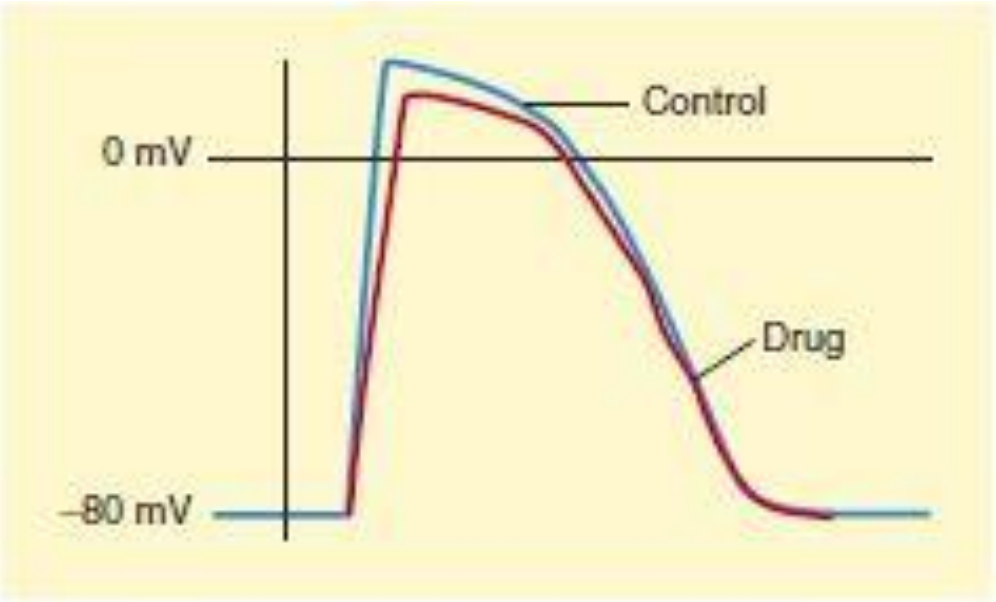
5. When working in outlying areas, this 62-year-old rancher is away from his house for 12–14 h at a time. He has an arrhythmia that requires chronic therapy. Which of the following has the longest half-life of all antiarrhythmic drugs?

A. Amiodarone
B. Lidocaine
C. Flecainide
D. Mexiletine

Questions

SAQ:

1. A drug was tested in the electrophysiology laboratory to determine its effects on the cardiac action potential in normal ventricular cells. The results are shown in the diagram.



Which drug does this agent most resemble? and 2 ADRS

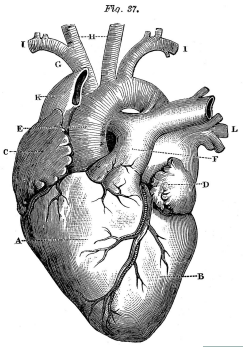
2. Which drug is most likely to block K+ channels in the heart responsible for cardiac repolarization, and also blocks calcium channels in the AV node? and 2 ADRS

3. A patient with a supraventricular tachycardia has an atrial rate of 280/min with a ventricular rate of 140/min via a 2:1 AV nodal transmission. After treatment with a drug, the atrial rate slowed to 180/min, but the ventricular rate increased to 180/min! Which of the following drugs was most likely to have been given to this patient? and 2 ADRS

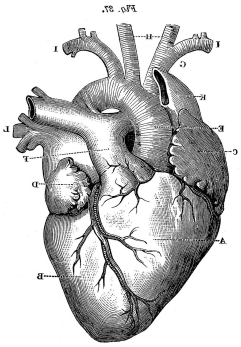
1. Flecainide. 1-Proarrhythmia 2-Heart failure
2. Amiodarone 1-Bradycardia & heart failure 2-Photodermatitis & skin deposits
3. Quinidine, 1-1. Hypotension 2. Quinidine syncope

MCQ Answers:

1. D
2. A
3. C
4. C
5. A



"It is not hard, you just made it to the end!"



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Thanks for those who worked on this lecture:

khaled aldosari
Anas Alsaif
Yazeed Alkhayyal
Omar Alyabis
Mohammed nouri
Fahad Alfaiz
Abdullah Alzahrani
Abdullah Alharbi
Adel Alsuhaibani
Fiasal Alhawtan

References:

✓ Doctors' notes and slides

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