

<R/Heads>PHARMACOLOGY

Drugs acting on the heart: antiarrhythmics

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Abstract

Arrhythmias are abnormalities of cardiac rate or rhythm occurring for a variety of reasons. They are common in the perioperative period and in intensive care. Causes may reflect an underlying heritable predisposition, the presence of new pathology either of the heart or conducting system, or as a result of systemic illness. Targets for antiarrhythmics include myocardial ion channels, muscarinic or nicotinic acetylcholine receptors, adrenergic or adenosine receptors.

Arrhythmias may cause cardiac arrest, and haemodynamic compromise, requiring rapid identification and corrective treatment either of rate or rhythm. Even where stable, arrhythmias present an increased risk of thromboembolic events requiring the use of anticoagulation.

Treatment may be directed at controlling heart rate or rhythm to restore the circulation and tissue perfusion. Strategies may include prevention or correction of precipitating factors (such as electrolyte abnormalities or sepsis) and sometimes non-pharmacological treatments (cardioversion, surgical ablation or pacing). Anti-arrhythmic drugs are often required. The targets, mechanisms and clinical guidelines are reviewed for common anti-arrhythmic agents.

Keywords amiodarone; anti-arrhythmia agents; arrhythmias, cardiac; digoxin; lidocaine; magnesium

Royal College of Anaesthetists CPD matrix: 1A02

Learning Objectives

After reading this article, you should be able to:

- draw the cardiac myocyte and pacemaker action potential, and note the effects of common antiarrhythmics on these
- list the major targets for antiarrhythmic actions
- identify at least five common causes of arrhythmias
- give named examples of the major classes of anti-arrhythmic drugs, along with their site and mechanism of action
- describe the evidence in relation to the treatment of common arrhythmias

Introduction

The myocardium contracts as a result of coupling to organised initiation and conduction of electrical activity (Figure 1). Myocardial muscle has gap junctions to facilitate conduction of electrical currents. The heart contains specialised conducting tissues, the His-Purkinje system, sino-atrial and atrioventricular nodes (SAN and AVN), which together enhance impulse initiation and transmission.

The depolarisation of the myocardial cells is initiated via the SAN. This pacemaker generates a depolarising impulse which passes to the AVN, the His-Purkinje system and finally to the ventricles. Arrhythmias are abnormal cardiac rhythms caused by abnormalities of impulse generation, impulse conduction or both. They may originate from any part of this system, and may be congenital or acquired in nature.

Some arrhythmias may cause little or no symptoms, but risk the formation of a malignant rhythm precipitating acute cardiovascular collapse. Patients who are otherwise well may tolerate some tachyarrhythmias that would otherwise cause symptoms of cardiovascular compromise in the critically ill, frail or those with impaired cardiac function. To understand arrhythmias and their treatment, it is helpful to review the normal electrophysiology of the cardiac myocyte and conducting system (Figure 1).

Classification

Antiarrhythmic drugs have traditionally been classified by the Vaughan-Williams system according to drug class and mode of action. However, this classification has limitations: it does not include all drugs with anti-arrhythmic properties, particularly newer agents, and some drugs have more than one action.

Table 2 gives a functional classification of anti-arrhythmic agents, showing site and mode of action as well as the arrhythmias for which the drugs are indicated.

Mechanisms of drug action – cardiac electrophysiology

Myocyte depolarisation causes Calcium influx and cellular contraction. The mechanism of excitation-contraction coupling is beyond the scope of this article, see Eisener, 2017 for a detailed review. Membrane potential is determined by the intra- and extracellular ratios of Potassium (K^+), Sodium (Na^+), and Calcium (Ca^{2+}). The resting membrane potential is maintained at $-60mV$ by the Sodium-Potassium ATPase pump. The voltage-gated ion channels in the myocyte and pacemaker cells cause distinct ion fluxes which cause characteristic changes in membrane potential in response to a depolarising stimulus (Figure 1).

In general, Na^+ or Ca^{2+} influx into myocytes and pacemaker cells causes the membrane potential to become less negative. Once this depolarisation reaches a threshold, further voltage-gated ion channels promote more rapid depolarisation and an action potential.

K^+ efflux promotes hyperpolarisation and membrane stability, reducing electrical activity. Most antiarrhythmics work directly or indirectly by blocking voltage-gated Na^+ or Ca^{2+} channels, ATPase pumps, or opening K^+ channels.

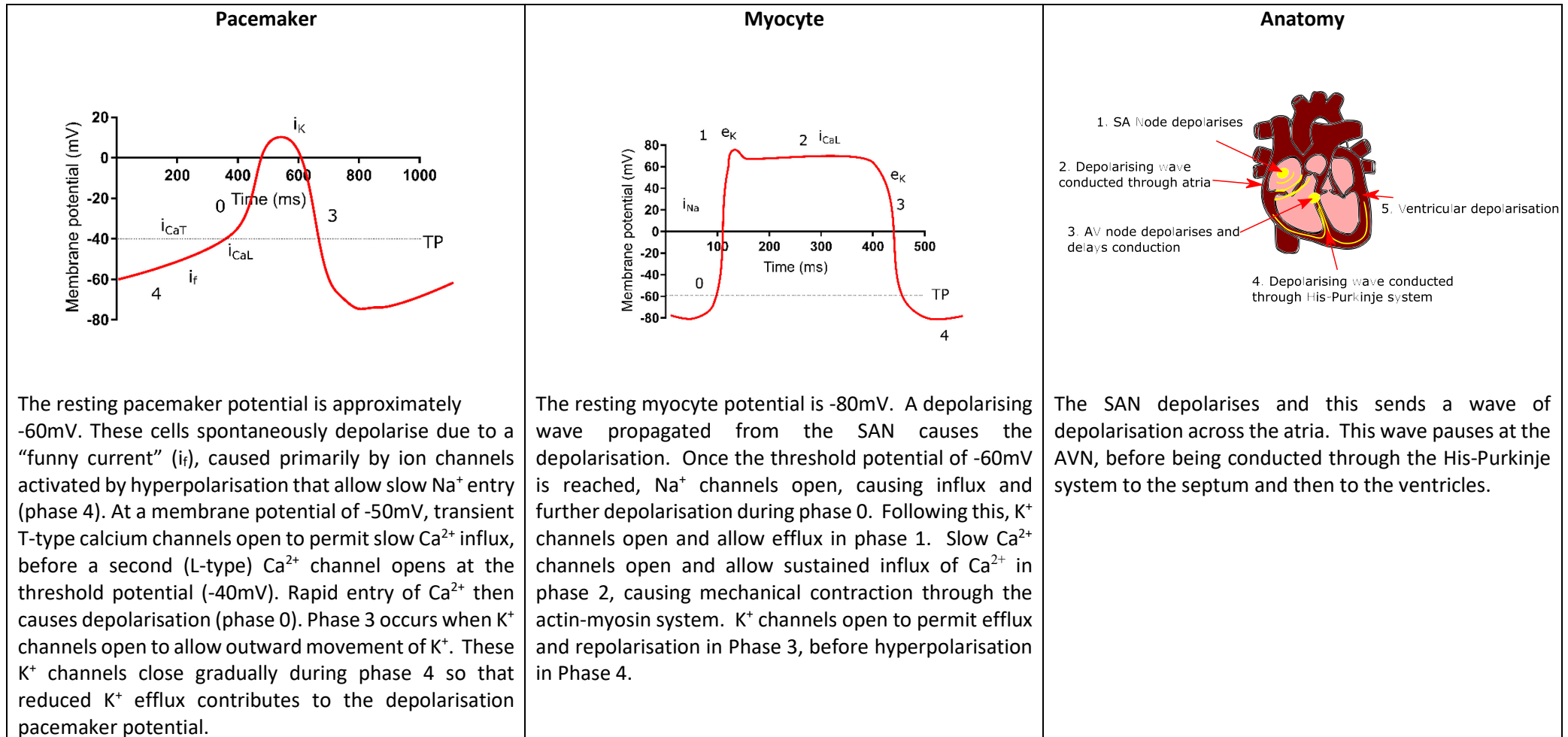



Figure 1 – link between myocardial contraction, electrical activity and contraction

The overall membrane potential is determined by the balance of intracellular and extracellular ion concentrations. Na^+ and Ca^{2+} influx contribute to depolarisation, whereas K^+ efflux contributes to hyperpolarisation and reduced excitability. Ca^{2+} and K^+ channels are influenced by autonomic nervous activity as well as hypoxia, temperature and drugs.



(ARP = Absolute refractory period, RRP = relative refractory period, TP = Threshold potential)

Antiarrhythmic targets within the myocardium

Hyperpolarisation causes reduced membrane excitability, and thereby reduces the occurrence of tachyarrhythmias. Increasing K^+ efflux, or reducing the influx of Na^+ or Ca^{2+} promotes myocardial stability through drug actions on voltage-gated K^+ , Na^+ and Ca^{2+} channels on the myocardium, conducting system, and in the SAN and AVN. Ca^{2+} channel blockers (e.g. *verapamil*), K^+ channel openers (e.g. *nicorandil*), and local anaesthetics (e.g. *lidocaine*) target these channels and are used in the management of arrhythmias. Non-specific therapies (such as magnesium) also modulate the activity of these channels. Na^+ and Ca^{2+} channel blockade opposes Phase 0 of the pacemaker potential, whereas enhanced K^+ channel activity enhances Phase 3 (Figure 1).

The myocardium is innervated by sympathetic and parasympathetic nerve fibres, which act via G-protein coupled receptors. β_1 adrenoceptors, coupled to G_s promote increases in intracellular calcium via cyclic-AMP and protein kinase C acting on L-type Ca^{2+} channels, and the "F" channels in pacemaker cells of the SAN. Blockade of β_1 adrenoceptors (e.g. by *metoprolol*) therefore reduces chronotropy, notropy and automaticity for the control of rate compromising tachyarrhythmias. Stimulation (e.g. by *isoprenaline*) increases rate and is used in the treatment of bradyarrhythmias prior to pacing.

Muscarinic M_2 receptors, linked to G_i proteins, cause reduced cAMP and activity of the L-type calcium and "F" channels, reducing heart rate. M_2 blockade (e.g. atropine or glycopyrrolate) is used in the treatment of bradyarrhythmias.

Cardiac myocytes express the adenosine A_2 ptor. A_2 receptor agonism by adenosine causes al blockade, and is used in the management of supraventricular tachycardias.

Which drug to use?

Where compromised, tachyarrhythmia in the presence of syncope, instability, chest pain or cardiac failure, the priority is to restore a perfusing rhythm by synchronised electrical cardioversion. For emergency treatment of acute arrhythmias within the hospital setting, current Resuscitation Council (UK) algorithms are available from www.resus.org.uk (1). Pulseless VT or VF is managed by defibrillation as per Resuscitation Council (UK) guidelines.

Where the arrhythmia is stable, non-pharmacological methods (carotid sinus massage or Valsalva manoeuvre), followed by drug therapy may terminate the arrhythmia. Underlying causes (Table 1) should always be corrected if possible.

For persistent or recurrent arrhythmias, where an electrophysiological or structural cause has been identified, interventional techniques (catheter ablation, implantable pacemakers/defibrillators) are preferred. These techniques are outside the scope of this article (see further reading: Macle 2015).

Chronic, stable arrhythmias may deteriorate to a rapid ventricular rate in critical illness, requiring additional rate slowing drugs or cardioversion.

Pharmacological management

The aims of rate control are to reduce myocardial oxygen demand by slowing ventricular rate, increasing the time for ventricular filling and coronary blood flow. The aim of rhythm control is to restore sinus rhythm and reduce the risk of deterioration to cardiac arrest, or of thromboembolic complications from intramural thrombus.

The UK Resuscitation Council guidance classifies tachyarrhythmias according to the width of the QRS complex and likely supraventricular or ventricular origin.

Supraventricular arrhythmias arise in the atria, SAN or AVN. The most common supraventricular tachycardia is atrial fibrillation with a rapid rate; supraventricular tachycardias include types of nodal, atrial or re-entrant tachycardias, and atrial flutter. If emergency electrical cardioversion is not required, rate control via nodal blocking drugs (Class I, II or IV), with the addition of digoxin in resistant cases is recommended by the European Society of Cardiology (2). Where this strategy fails, amiodarone is suggested. Adenosine causes nodal blockade and can be useful in the treatment of nodal arrhythmias.

Broad complex tachycardias may originate in the ventricles or supraventricular tissues with a conduction delay. Arrhythmias of supraventricular or nodal origin are managed as above.

Ventricular arrhythmias represent abnormal foci of electrical activity in the ventricles or abnormal pathways through fast and slow conducting tissue. Broad complex tachycardias have significant risk of deteriorating to cardiac arrest, and rhythm control by cardioversion is a priority. Class I and III agents target ion flux, whereas amiodarone and magnesium promote membrane stability.

In the case of pulsed VT, goals are to restore sinus rhythm, and reduce the risk of cardiac arrest and sudden cardiac death either through electrical or pharmacological cardioversion. Underlying causes include inheritable molecular arrhythmogenic conditions, and congenital or acquired structural heart defects requiring specific preventative management directed at the underlying cause; this is beyond the scope of this article.

Drugs to treat tachyarrhythmias

The effect of reduced myocardial electrical conduction induced by these drugs can induce complete heart block, malignant arrhythmias or cardiovascular collapse.

Sodium channel blockers (Vaughan-Williams Class I)

Class I antiarrhythmics block voltage-gated Na^+ channels to reduce the excitability of electrically active tissues. They are further subclassified by effect on the refractory period with Ia and Ib, lengthening and shortening this respectively, whereas class Ic drugs have no effect on the refractory period. *Lidocaine* (Ib) is indicated for ventricular arrhythmias as an alternative to amiodarone. *Flecainide* (Ic) can be used for cardioversion of fast supraventricular arrhythmias, although it is contraindicated in the presence of structural heart disease.

Beta blockers (Vaughan-Williams Class II)

Beta blockers antagonise the β_1 adrenoceptors, coupled to G_s with varying degree of cardioselectivity, speed of onset and potency. Short lived drugs (e.g. *esmolol*) are useful to cardiovert or unmask an underlying rhythm, whereas longer acting agents may be used intravenously for rapid rate control (e.g. *metoprolol*). Longer acting drugs are used for chronic rate control (e.g. *bisoprolol*). Older agents had some crossover β_2 activity (eg. *carvedilol*, *propranolol*) and may precipitate bronchospasm. Newer agents exhibit a higher degree of β_1 selectivity and avoid this (e.g. *bisoprolol*, *metoprolol*, *atenolol*).

Potassium channel openers (Vaughan-Williams Class III)

This class contains a range of drugs, many of which act on multiple ion channels to promote membrane stabilisation for both supraventricular and ventricular arrhythmias. The commonest used in the management of acute arrhythmias is amiodarone. For longer term management, *sotalol* is often used. This class is often used in cardiac surgical patients where other drugs may be ineffective. *Vernakalant* and *Azimilide* are examples of Class III drugs used in this group.

Amiodarone is classified as class III, although also has mechanisms common to class I, II and IV drugs and affects Na⁺ and K⁺ channels and β-adrenoceptors. Na⁺ channel blockade causes hyperpolarisation at the SAN and AVN, prolonging the refractory period and action potential. K⁺ channel blockade also prolongs the refractory period in pacemaker and myocyte cells (Figure 1). β-adrenoceptor blockade has a negative chronotropic effect at the SAN. This multimodal effect is suited to both supraventricular and ventricular arrhythmias. It is metabolised by the liver to an active metabolite. It has many adverse effects during chronic administration, most notably pulmonary fibrosis, corneal micro deposits, thyroid disorders, cirrhosis and peripheral neuropathy. During acute administration, it can precipitate cardiovascular collapse and AV block. *Dronedronone* is an analogue of amiodarone and shares the same mechanism. It is recommended for the maintenance of sinus rhythm in paroxysmal atrial fibrillation refractory to other antiarrhythmics and has a more favourable side effect profile than amiodarone.

Ibutilide is a pure class III drug acting on slow inward Na⁺ channels, reducing the slope of Phase 0, thereby prolonging the action potential and refractory period. Ibutilide is commonly used for recent-onset AF. It is administered as an intravenous infusion over 10 minutes and repeated if necessary; the dose is dependent on body mass (0.01 mg kg⁻¹ as a slow IV bolus over 10 minutes, repeatable for one further dose). It is metabolised by hepatic cytochrome P450 enzymes; adverse effects include chest pain and breathing difficulties.

Calcium channel antagonists (Vaughan-Williams Class IV)

Verapamil and *Diltiazem* are both used for supraventricular arrhythmias. They both have nodal blocking properties by antagonising the slow (T-type) Ca²⁺ channel, affecting Phase 0 of the pacemaker potential. This decreased Ca²⁺ influx decreases automaticity and increases the refractory period. They can be used acutely to cardiovert or rate control, and are also used for chronic management. Adverse effects include first- or second-degree heart block and VT/VF in patients with Wolff–Parkinson–White syndrome (WPW).

Other drugs (Vaughan-Williams Class V)

Adenosine: a naturally occurring purine nucleoside that acts at specific A₁ and A₂ receptors in the atria. The effect in electrically active tissue is to induce hyperpolarisation by opening K⁺ channels, which are coupled to the A₁ receptor via G_i. Hyperpolarisation of the SAN, AVN and conduction pathways induces a transient AV block, which may either cause cardioversion, or slow the heart rate to enable interpretation of the underlying rhythm. Enhancing K⁺ efflux reduces the electrical excitability in pacemaker cells and myocytes (Figure 1), thereby stabilising cardiac rhythm. Adenosine has a half-life of 10 seconds, and is given as a rapid intravenous bolus in escalating doses of 6mg followed by 12mg and a final dose of 12mg. Hyperpolarising normal electrically active tissue may enhance conduction along accessory pathways, and therefore it is contraindicated in WPW. Relative and absolute contraindications include asthma, sick sinus syndrome, decompensated heart failure, heart blocks and long Q-T syndrome. Due to the risks of profound bradycardia or potentiating arrhythmias, adenosine must be given with continuous cardiac monitoring. Selective A₁ agonists (*tecadenoson* and *selodensoson*) are in development to avoid the adverse effects produced by nonspecific A_{2A}, A_{2B} and A₃ adenosine receptors.

Digoxin: a glycoside that has direct and indirect effects. The direct effect is through inhibition of the Na⁺/K⁺-ATPase. This prolongs the refractory period, thereby increasing [Na⁺]_i and decreasing [K⁺]_i. Digoxin also enhances vagal activity causing indirect negative chronotropic effects. An additional effect is to increase [Ca²⁺]_i, increasing inotropy. This combination of effects is commonly used to treat atrial fibrillation and flutter, often as combination therapy.

The narrow therapeutic range of digoxin requires a loading regimen, dose monitoring and caution in renal failure. Therapeutic plasma concentrations must be monitored as digoxin toxicity causes several adverse effects, including junctional bradycardias, ventricular bigeminy, second- and third-degree heart block and visual disturbances. The dose is reduced in patients with renal failure, and toxicity is increased in the presence of hypokalaemia, hypomagnesaemia, hypernatraemia or hypercalcaemia. The loading dose of digoxin is 10–20 µg kg⁻¹ (orally or parenterally) in three divided doses at 6-hour intervals until the desired effect has been established, followed by maintenance doses of 10–20 µg kg⁻¹ day⁻¹.

Magnesium: a cofactor in many enzyme systems including the Na⁺/K⁺-ATPase. It antagonises atrial Ca²⁺ channels and inhibits K⁺ channels, causing an increase in the refractory period. It is used to treat torsades de pointes and ventricular arrhythmias. Various dosing regimens exist (e.g. 16 mmol over 20 minutes intravenously), however the dose should be titrated to pre-existing Mg²⁺ levels and serum Mg²⁺ concentrations should be monitored closely. Fifty percent is excreted unchanged in the urine. Adverse effects include AV and intraventricular conduction disorders as well as muscular and respiratory weakness. Toxic effects of hypermagnesaemia can be overcome by administration of calcium.

Table 1 (Reset table per style)

Physiological	Biochemical	Disease
Cardiac ischaemia	Hypo/hyperkalaemia	Sepsis
Hypotension	Hypocalcaemia	Pneumonia
Autonomic dysfunction	Hypomagnesaemia	Pericarditis
Hypoxia	Drugs (e.g. epinephrine, TCADs)	Myocarditis
Hypercapnia		
Hyper/hypothyroid		
Hypothermia		
Vagal		
Increased ICP		

ese, when known. Correction of these factors alone may be sufficient to restore a normal rhythm, but in addition the efficacy of anti-arrhythmic drugs
 ple, increased vagal tone can occur during stimulation/retraction on the peritoneum, extraocular muscles or uterine cervix. Uncontrolled sympathet-
 hesia. The management of vagal bradycardias is to release the traction/stimulation of these areas and administer a vagolytic, e.g. atropine (600 µg)
 the cardiac output or blood pressure compromised, or is this a precursor of a more serious dysrhythmia?. For emergency treatment of acute arrhyth-
 algorithms¹ are available from www.resus.org.uk.
 triocytic antidepressants; ICP, intracranial pressure.

Table 2. Indications, classification and mechanisms of action of anti-arrhythmic drugs

Drug class/mechanism of action	Site of action	Vaughan-Williams	Example	Electrophysiological effects	Uses	Adverse effects
Sodium channel blockade	Conducting system	Ia	Quinidine Dysopyramide Procainamide	↑ refractory period ↑ AP duration ↑ QRS duration	SVT, VT, atrial tachyarrhythmias WPW	Arrhythmias, Torsades de pointes
	Conducting system	Ib	Lignocaine Tocainamide Mexiletine	↓ refractory period ↓ AP duration ↔ QRS duration	VF/VT during ischaemia	Hypotension, Heart block, Confusion, Seizures
	Conducting system	Ic	Flecainide Propanenone Morcizine	↔ refractory period ↔ AP duration ↑ QRS duration	Conversion / prevention of VT/VF/SVT	Arrhythmias
Beta-blockers	SAN AVN	II	Bisoprolol Atenolol	↓ automaticity	Prevention of sympathetically mediated arrhythmias	Bronchospasm, Heart block
Potassium channel blockers	Myocardium	III	Amiodarone Sotalol Ibutilide	↑ refractory period ↑ AP duration ↔ QRS	Prevention of VT/VF/SVT	Arrhythmias Amiodarone specific: corneal deposits, deranged LFTs, Hypothyroidism
Calcium channel blockers	SAN AVN	IV	Verapamil	↓ AP duration ↓ refractory period ↓ pacemaker depolarisation	Rate control in AF Prevention of AVNRT	Heart block Hypotension
Purines	Adenosine receptors	NA	Adenosine	↓ SAN activity ↓ AVN activity ↑ e _k	Diagnosis and treatment of paroxysmal SVT	Arrhythmias Bronchospasm
Cardiac glycosides	AVN	NA	Digoxin	Enhance vagal activity Slow nodal CV Block Na ⁺ /K ⁺ -ATPase Increase calcium availability	Treatment of AF / flutter	Arrhythmias, Fatigue, Nausea, Confusion

CV = Conduction Velocity, AP = Action Potential, SAN = Sino-Atrial node, AVN = Atrioventricular Node, e_k = Potassium efflux, WPW = Wolff-Parkinson-White

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