

Drugs in Cardiology

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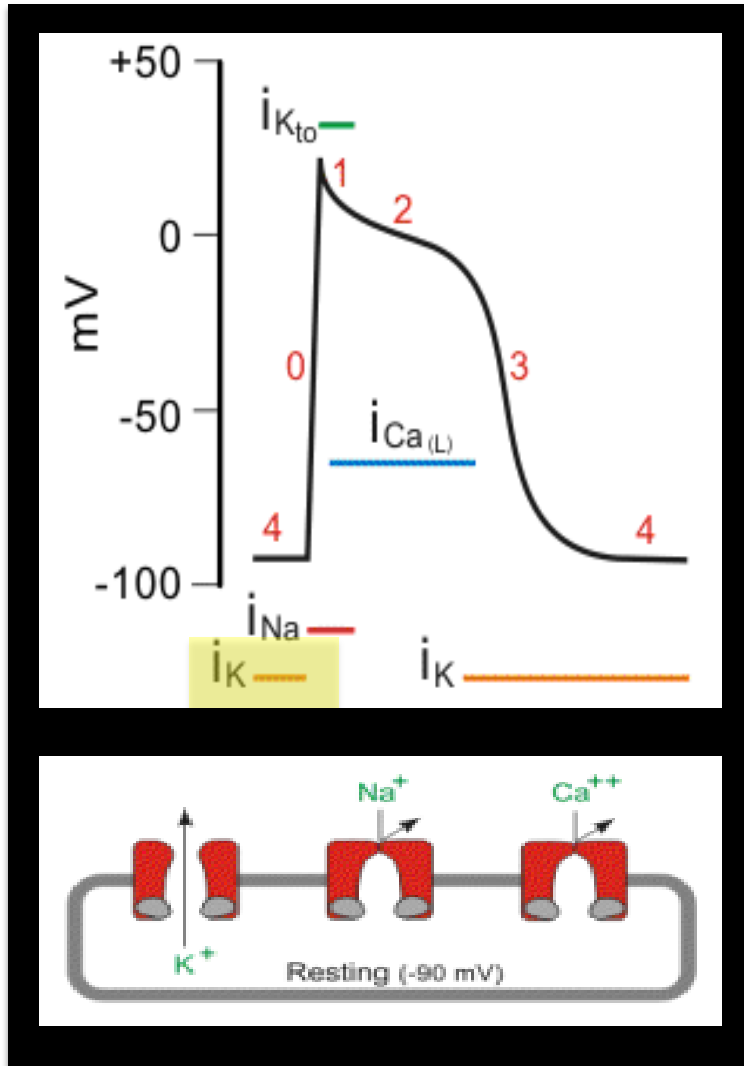
What do you need to know about pharmacology for BHRs exam

PHARMACOLOGY

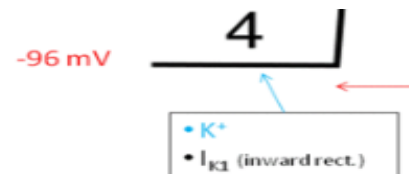
Action, duration of action, side effects, interactions and contra-indications of drugs used in the management of arrhythmias and heart failure including the Vaughan Williams classification, proarrhythmic effects, potential effect of drugs on implantable device function, agents used for moderate sedation, reversal agents, antibiotics, anticoagulation, pharmacological provocation e.g. isoprenaline, ajmaline and the management of heart failure e.g. role of beta-blockers, ACE inhibitors.

- Cardiac action potential
- Vaughn William's classification
- Effects of drugs on pacing thresholds and DFTs
- Indications for different drugs
- Side effects of drugs
 - QT interval
 - Toxicity
 - contraindications
- Drugs for heart failure

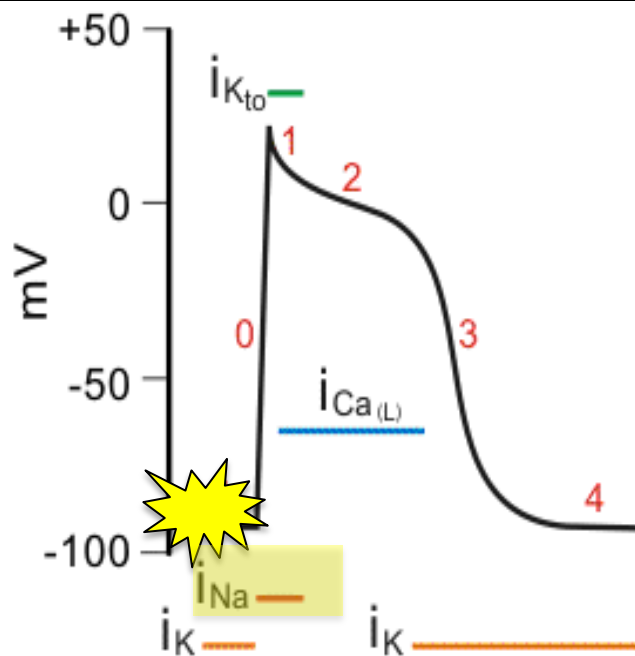
Phase 4 (Cardiomyocyte AP)



- Phase 4= **Resting membrane potential**
 - Horizontal line (non-pacemaker cells)
 - -90mV
- In phase 4 membrane most permeable to K^+ ions
 - Fast Na^+ channels and slow Ca^{2+} channels are closed
- Stable vs. unstable phase 4

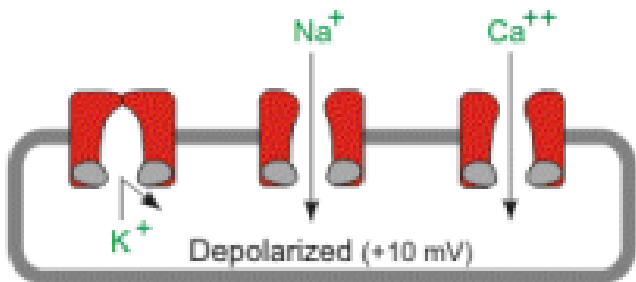


Phase 0 (depolarisation)

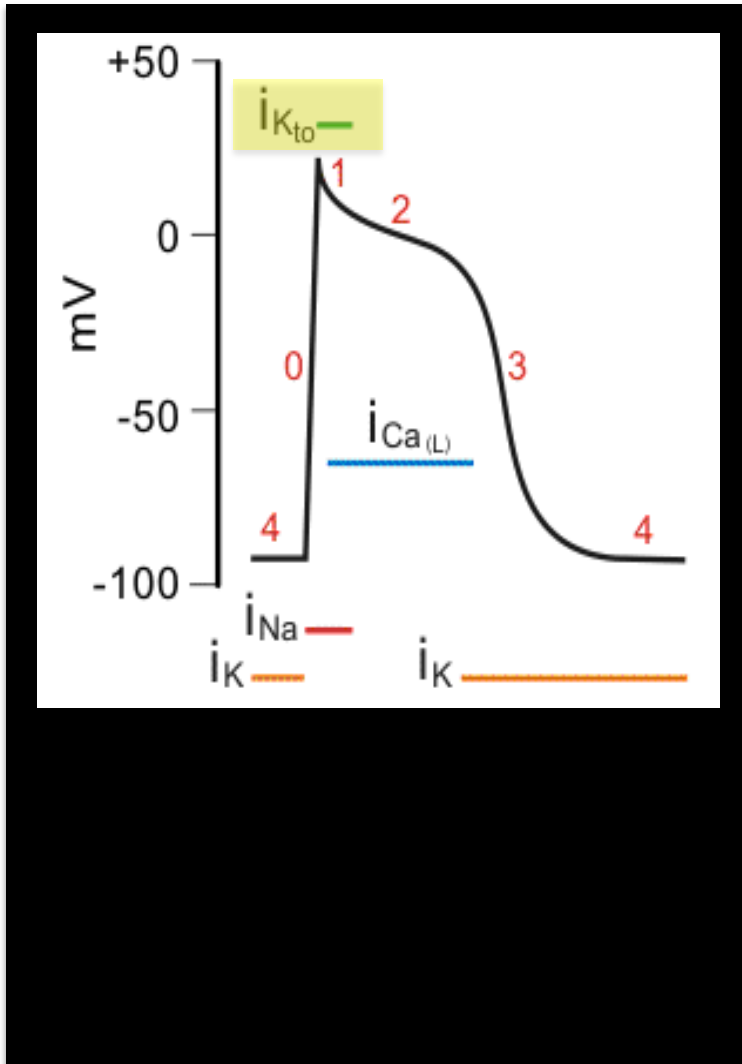


Phase 0=rapid depolarisation

- Electrical stimulation of cell by adjacent cell undergoing depolarisation
 - The K^+ channels are closed during phase 0
 - Opening of **Fast Na^+ channels**
 - Influx of Na^+
 - Increase in membrane potential
- Potential inside the cell rises to +10mV

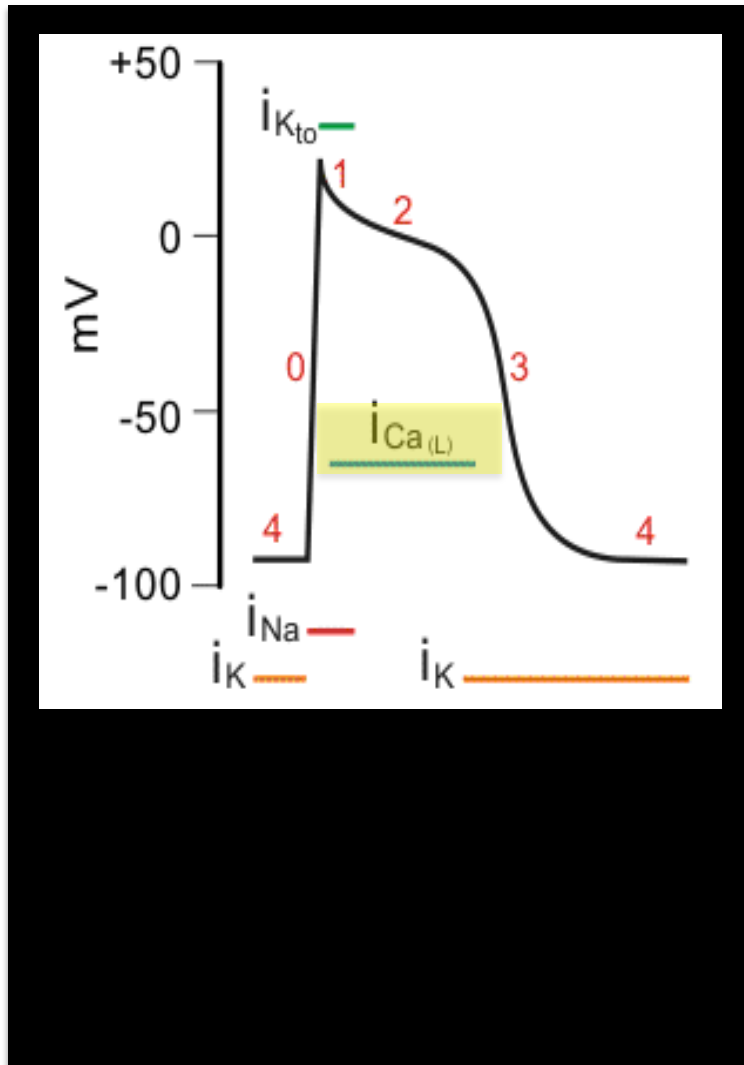


Phase 1 (initial repolarisation)



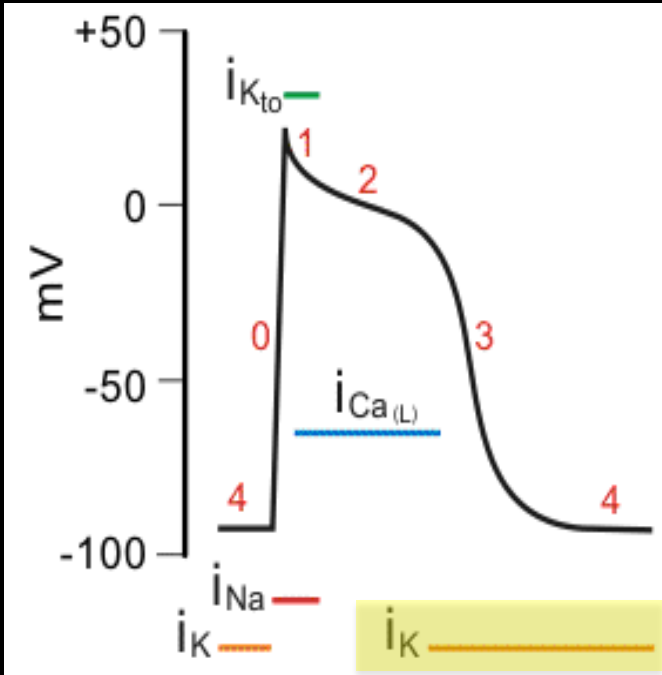
- **Phase 1 represents initial repolarisation**
- Closure of fast Na⁺ channels
- Net outflow of K⁺
 - caused by opening of transient outward K⁺ channel (K_{to})
 - **hyperpolarising outward K⁺ current ($i_{K_{to}}$)**

Phase 2 (plateau phase)



- **Phase 2** represents the “plateau phase”
- Sustained by:
 - **Inward movement of calcium** through **Slow (L-type) calcium channels**
 - Slow outward movement of K^+ thru the **slow delayed rectifier K^+ channel**
- Phase 2 differentiates cardiomyocyte action potentials from those of pacemaker cells, skeletal muscle and nerves

Phase 3 (rapid repolarisation phase)

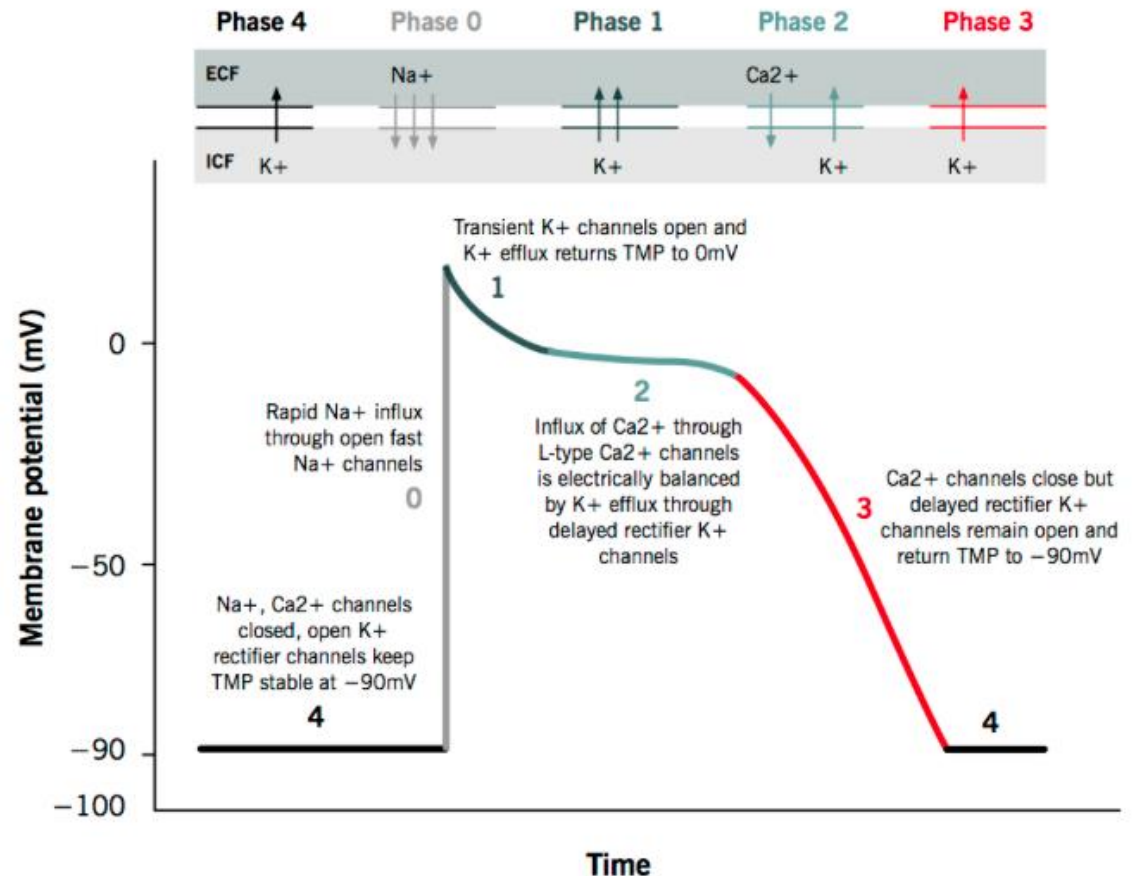


- During phase 3, L-type Ca^{2+} channels close while **delayed rectifier K^+ channels remain open**
- Net outward movement of current (loss of positive charge from the cell)
 - Increasingly -ve membrane potential
 - Cell repolarises
- Delayed rectifier K^+ channels close when membrane potential reaches approximately -80mV

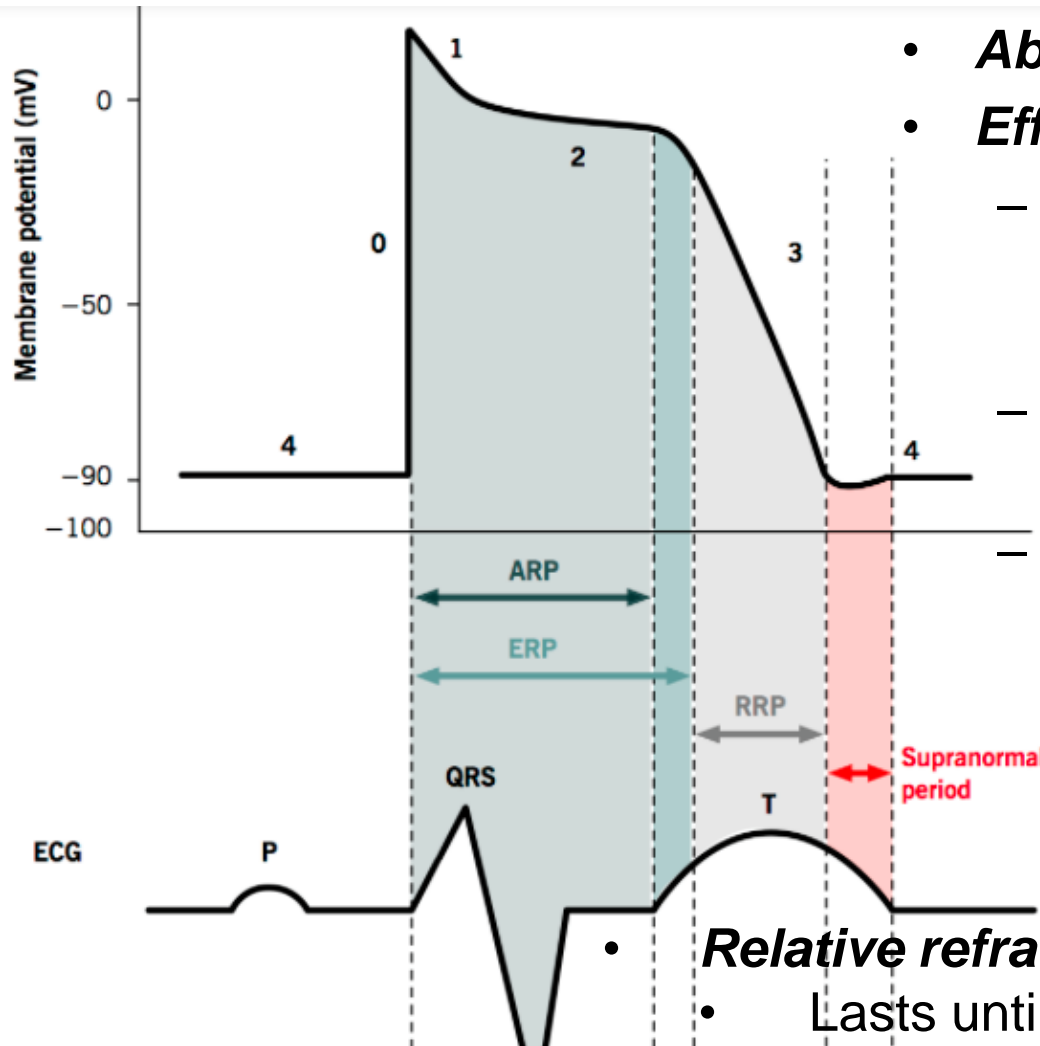
Phase 4



- -90mV resting membrane potential
- Action potentials are ***all or nothing events***
- Threshold of -70 mV required before depolarisation of the cell is initiated



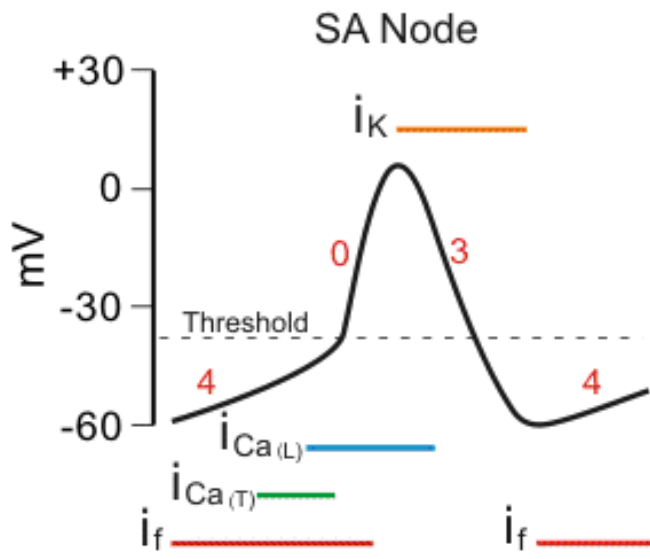
Refractory periods



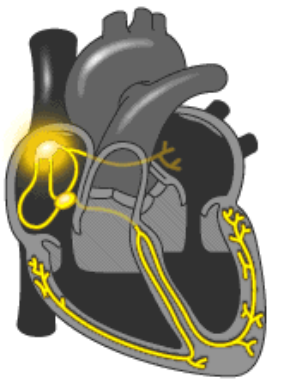
- ***Absolute refractory period***
- ***Effective refractory period***
 - ERP and (action potential duration) APD are closely correlated
 - During ERP it is impossible to evoke another action potential
 - Protective mechanism

- ***Relative refractory period***
 - Lasts until the end of phase 3
 - During this time only a stronger than usual stimulus can depolarise the cell

Sinoatrial node action potential



- Excitatory (pacemaker) cells have an unstable phase 4
- No true resting potential
 - Automaticity
- No phase 2
- I_f (funny) channels
 - Site of action of ivabradine



Vaughn Williams classification

Classified on the basis of
their cellular
electro-physiologic
properties into 5 classes
– (I-V)

DRUG	CHANNELS										RECEPTORS					PUMPS	CLINICAL EFFECTS						
	Na					Ca	K	I _K	α	β	M ₂	A ₁	Na-K ATPase	ECG axis deviation	Arrhythmia		Extra-systolic	PR	QRS	QT			
	Fast	Mod	Slow																				
Lidocaine	○														→	→	⊗			↓			
Mexiletine	○														→	→	⊗			↓			
Tocainide	○														→	→	●			↓			
Moricizine	I														↓	→	○		↑				
Procainamide		A			⊗										↓	→	●	↑	↑	↑			
Disopyramide		A			⊗						○				↓	→	⊗	↑	↑	↑			
Quinidine		A			⊗				○			○			→	↑	⊗	↑	↑	↑			
Propafenone		A							⊗						↓	↓	○	↑	↑				
Flecainide			A												↓	→	○	↑	↑				
Encainide			A												↓	→	○	↑	↑				
Begiridil	○				●	⊗									?	↓	○			↑			
Verapamil	○				●				⊗						↓	↓	○	↑					
Diltiazem					⊗										↓	↓	○	↑					
Bretylum						●		▲	▲						→	↓	○			▲			
Sotalol						●				●					↓	↓	○	↑		▲			
Amiodarone	○				○	●		⊗	⊗						→	↓	●	↑		▲			
Alinidine						⊗	●								?	↓	●						
Nadolol										●					↓	↓	○	↓					
Propranolol	○									●					↓	↓	○	↑					
Atropine											●				→	↑	⊗	↓					
Adenosine															?	↓	○	↑					
Digoxin													●		↑	↓	●	↑		↓			

Relative potency of block: ○ Low ⊗ Moderate ● High

○ = Agonist ▲ = Agonist/Antagonist

I = Inactivated state blocker

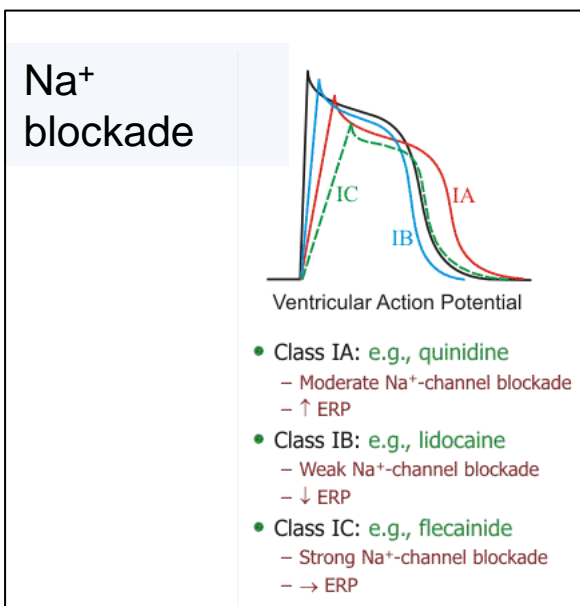
A = Activated state blocker

Relative potency of block: Low (○) Moderate (○) High (●)
 A = Activated state blocker
 I = Inactivated state blocker
 ○ = Agonist ▲ = Agonist/Antagonist

CLASS I ANTI-ARRHYTHMICS

Na channel blockers

- Bind to fast Na⁺ channels responsible for phase 0 depolarisation
- Strong/moderate /weak Na⁺ channel blockade
- Rapid depolarisation is reduced according to strength of Na⁺ blockade
- Class I agents also exert varying effects on **K⁺ channels** (phase 3)
 - Class 1 agents have differential effects on **ERP** and **APD**



CLASS I AGENTS: SUMMARY

- Class 1 agents

Na⁺ channel blockade

C >> A >> B



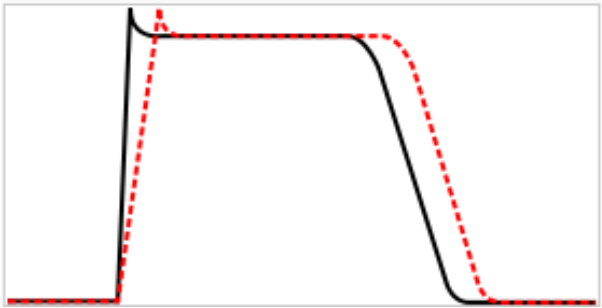
K⁺ channel blockade

	1A	1B	1C
ERP	↑	↓	↔

QT interval is a function of action potential duration
ERP/ APD and QTc are closely correlated*

Class IA agents prolong the APD and QTc the most.

CLASS 1A AGENTS



Quinidine, procainamide, disopyramide

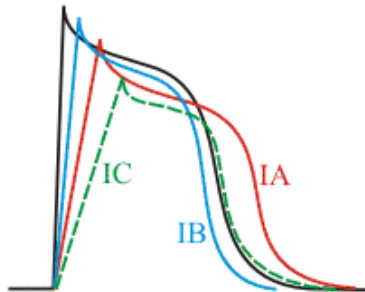
- Maintenance of SR in patients with PAF
- VT

- **Moderate Na⁺ channel blockade**

- Moderately prolong phase 0 (C>A>B)

- **Increase ERP**

- Can also cause arrhythmias = pro-arrhythmic
 - **QT prolongation**
 - TDP



Ventricular Action Potential

- Class IA: e.g., quinidine
 - Moderate Na⁺-channel blockade
 - ↑ ERP
- Class IB: e.g., lidocaine
 - Weak Na⁺-channel blockade
 - ↓ ERP
- Class IC: e.g., flecainide
 - Strong Na⁺-channel blockade
 - → ERP



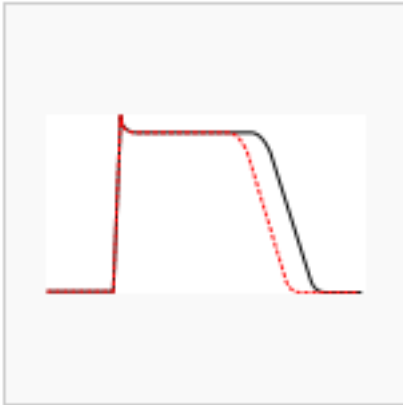
DISOPYRAMIDE

- Indicated for maintenance of sinus rhythm in patients with pAF; treatment of VT
- Adverse effects include proarrhythmic effect (exacerbated by hypokalaemia), hypotension
- Negative inotrope
- Anticholinergic side effects

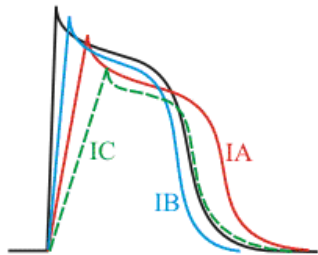
PROCAINAMIDE

- Indicated for treatment of pAF and VT
- **Long-term oral use associated with SLE-like syndrome in 25 – 30%**
 - **Bone marrow suppression**
 - Proarrhythmic

CLASS 1B AGENTS



Class Ib



Ventricular Action Potential

- Class IA: e.g., quinidine
 - Moderate Na⁺-channel blockade
 - ↑ ERP
- Class IB: e.g., lidocaine
 - Weak Na⁺-channel blockade
 - ↓ ERP
- Class IC: e.g., flecainide
 - Strong Na⁺-channel blockade
 - → ERP

Lidocaine, mexiletine (phenytoin)

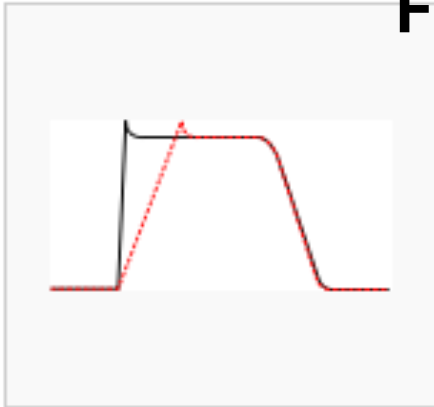
- VT
 - Good efficacy in treating ischaemic VT
- (C>A>B) Weak Na⁺ channel blockade
- Decrease effective refractory period
- Decrease APD
- Decrease the QT interval

LIDOCAINE AND MEXILETINE

- Indicated for treatment of VT
- **Adverse effects include CNS side effects- agitation, tremors, hallucinations, psychosis (lidocaine)**
- **Mexiletine**, Good oral bioavailability
 - can cause nausea and headache

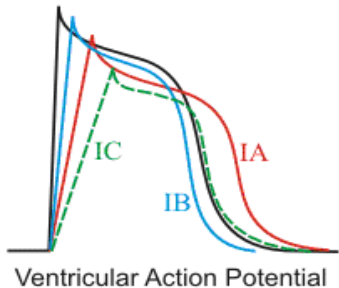
CLASS 1C AGENTS

Flecainide, propafenone



- Treatment and prevention of PAF (structurally normal hearts)
- SVT (prolongs retrograde refractoriness of fast pathway)
- Accessory AV pathways (refractoriness of AP)

Class 1c



- Class 1A: e.g., quinidine
 - Moderate Na⁺-channel blockade
 - ↑ ERP
- Class 1B: e.g., lidocaine
 - Weak Na⁺-channel blockade
 - ↓ ERP
- Class 1C: e.g., flecainide
 - Strong Na⁺-channel blockade
 - → ERP

- **Strong Na⁺ channel blockers**
 - significantly prolong phase 0 (**C**>**A**>**B**)
 - Use dependence = increased effect at higher HR
- Little effect on phase 3/ERP
- Can also cause arrhythmias (pro-arrhythmic effect), specifically VT/ TDP
- **1:1 conduction of atrial flutter**
 - **Concomitant use of B- blocker reduces risk of 1:1 conduction**

FLECAINIDE

- Indicated for treatment of pAF, SVT and occasionally used in VT (in patients without structural heart disease)
- Avoid in CAD and LVSD
- Flecainide challenge in suspected Brugada
- Adverse effects include proarrhythmic effect
 - **Toxicity associated with PR /QRS and QT prolongation**
- CNS effects in 10-15% (headache, dizziness)
- Metallic taste

PROPAFENONE

- Indicated for treatment of SVT and VT (in patients without structural heart disease)
- Adverse effects include proarrhythmic effect
- Also has B-blocking and Ca²⁺ channel blocking activity
- Avoid in CAD/LVSD

Cardiac Arrhythmia Suppression (CAST) Trial

- Use of class IC agents to suppress asymptomatic ventricular arrhythmias post MI
 - 2300 patients, prior MI, ≥ 6 ectopics/hr
 - Randomised to flecainide, encainide, moricizine or placebo
- Increased mortality in patients treated with flecainide and encainide group compared to placebo (4.5% vs. 1.2%)**
- Recommendations for 1C drugs:
 - Structurally normal heart
 - Not used in patients with IHD
 - Not used in patients with LVSD

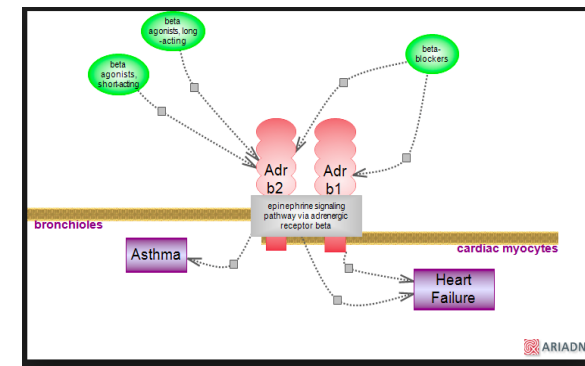
CLASS II ANTIARRHYTHMIC AGENTS

Beta- Blockers

- Bind to B-adrenoceptors blocking binding of adrenaline and noradrenaline
 - Block sympathetic activity
 - Inhibits phase IV depolarisation in SAN and AVN
- Some are relatively selective for B1-adrenoceptors (cardiac)
 - Fewer peripheral side effects

ANTIARRHYTHMIC EFFECTS

- Negative inotropes, chronotropes and dromotropes
- Decrease conduction velocity
- **Increase action potential duration and ERP**



CLINICAL USES OF COMMONLY USED B-BLOCKERS

Class/drug	HTN	ANGINA	ARR	MI	CCF	COMMENTS
NON-SELECTIVE B1/B2						
CARVEDILOL						
LABETOLOL						
NADOLOL						LONG ACTING, water soluble
PROPRANOLOL						Lipid soluble
SOTOLOL						Water soluble, class II effects
TIMOLOL						Used mainly for glaucoma
B1 SELECTIVE: less effect on B2 receptors and relatively cardioselective						
ATENOLOL						Water soluble
BISOPROLOL						
ESMOLOL						Ultra short-acting
METOPROLOL						Lipid soluble

CLASS II ANTIARRHYTHMIC DRUGS (B-ADRENOCEPTOR ANTAGONISTS)

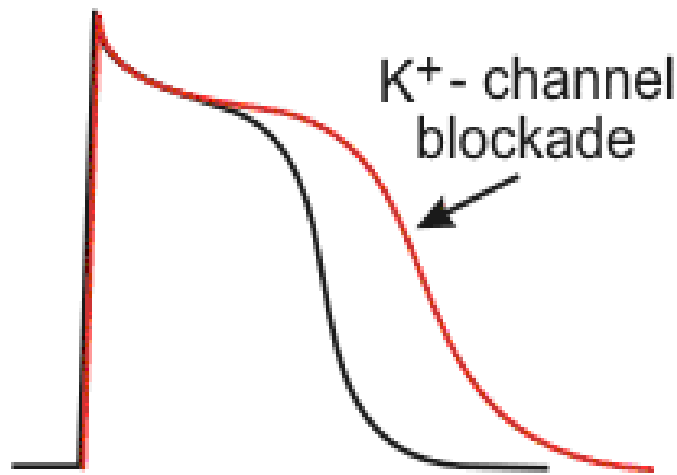


Side effects of Beta blockers

- **BBC Viewers In Revolt**
 - Bradycardia
 - Bronchoconstriction
 - Claudication
 - Vivid dreams and nightmare
 - -ve Inotropic action
 - Reduced sensitivity to hypoglycaemia

CLASS III ANTIARRHYTHMICS

Delayed Repolarization by
Potassium-Channel Blockade



Ventricular Action Potential

**Amiodarone, dronedarone,
bretylum, dofetilide,
sotalol**

- Bind and block K⁺ channels responsible for repolarisation
- Increase in action potential duration
- QT interval increased on ECG

AMIODARONE ACTION & SE

Amiodarone has class I-IV properties

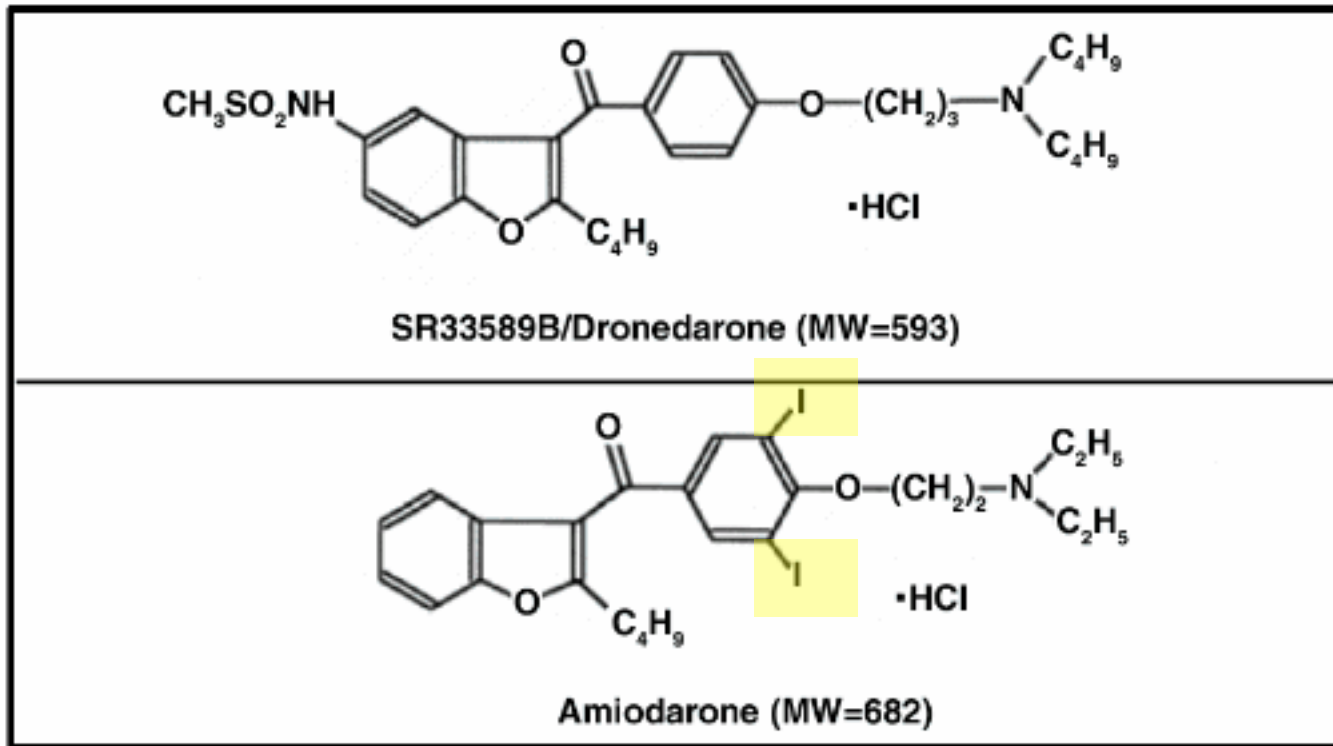
6 P's:

- **P**rolongs action potential duration
- **P**hotosensitivity
- **P**igmentation of skin (blue-grey)
- **P**eripheral neuropathy
- **P**ulmonary alveolitis and fibrosis
- **P**eripheral conversion of T4 to T3 is inhibited
-> hypothyroidism

SOTOLOL

- Class II and III properties
- Racemic mixture of d- and l- isomers (1:1 ratio)
- Both isomers possess class III antiarrhythmic effects
- 97% of **B-blocking** activity possessed by l-isomer
- Class III action not exhibited below doses of 80mg b.d.
- Pro-arrhythmic effect exacerbated by hypokalaemia
- QT prolongation a significant risk

Dronedarone vs. Amiodarone



Similar electrophysiological properties to amiodarone

Unlike amiodarone it does not contain iodine

Dronedarone trials: Andromeda

DESIGN

- 627 patients with symptomatic heart failure, randomised to dronedarone or placebo

RESULTS

- Terminated after 7 months
- 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07 to 4.25; $p=0.03$). The excess mortality was predominantly related to worsening of heart failure

Dronedraone trials: PALLAS

Pallas

(Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

- 3236 patients with permanent AF and risk factors for major vascular event randomised to dronedarone or placebo
 - Primary endpoint was stroke, MI, systemic embolism or death from cardiovascular causes
- Terminated after one year by safety committee
- Significant increase in heart failure, stroke and death from cardiovascular causes with dronedarone

Class IV agents: Calcium channel blockers

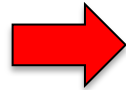
Verapamil and diltiazem

- Block L-type calcium channels
- Decrease conduction through the SAN and AVN
- Negative inotropy, negative chronotropy, negative dromotropy
 - Both agents can cause significant hypotension when given in large doses

Calcium channel blockers

- **Dihydropyridines**

- Amlodipine
- Felodipine
- Nifedipine



*Mainly affect vascular L-type calcium channels on smooth muscle and lower BP:
Antihypertensives*

- **Non-dihydropyridines**

- Verapamil (phenylalkylamine)
- Diltiazem (benzothiazepine)



*Cardiac L-type calcium channels
(negative inotropy++)*

*Potent vasodilator also
- Negative inotropic, chronotropic
and dromotropic effect)*

Contraindications:

- Acute heart failure with systolic dysfunction
- WPW and pre-excited AF
- Broad complex tachy
- do not use with B-Blockers



Digoxin

Cardiac glycoside derived from digitalis

- Inhibits Na^+/K^+ -ATPase and increase intracellular sodium concentration
- Negative chronotropic and negative dromotropic effects
- Positive inotropic effects
- Caution in hypokalaemia

Contraindications:

Hypokalaemia

Hypomagnesaemia

Don't use in Pre-excited AF (WPW)/ cardiac amyloidosis

Caution in renal impairment

High levels= toxicity and heart block

Xanthopsia

GI upset

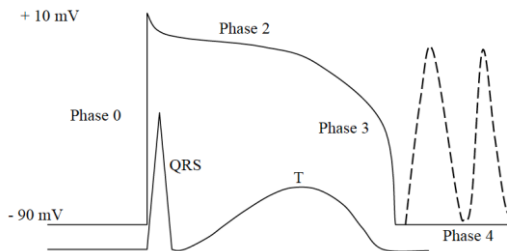
N+V

Adenosine

- AV node blocking agent used in the treatment of SVTs and the diagnosis of arrhythmias
 - Also a vasodilating agent
- Transient heart block
- Short acting
- SE = bronchospasm
- Caffeine and theophyllines antagonise adenosines effects
- Dipyridamole potentiates effects of adenosine
 - Either give less adenosine
 - Anticipate longer pause
- Contraindications
 - Asthma
 - Heart block
 - WPW with AF.

QT prolongation

- Class 1a and C drugs
 - Quinidine and procainamide
 - Flecainide* and propafenone
- Class III agents also associated with QTc prolongation
 - Sotalol
 - Amiodarone
 - dofetilide



Antiarrhythmics Associated with QT prolongation				
Amiodarone	Definite	High	QT, TdP	i.v. affects QTc less than oral; proarrhythmia infrequent.
Adenosine	Proposed	–	–	
Disopyramide	Definite	High	QT, TdP	Rate appears lower than that of quinidine.
Dofetilide	Definite	High	QT, TdP	Proarrhythmia 0.8%.
Flecainide	Definite	–	QT, TdP	Proarrhythmia "rare."
Ibutilide	Definite	High	QT, TdP	Proarrhythmia 1.7%.
Procainamide	Definite	High	QT, TdP	Rate appears lower than that of quinidine.
Propafenone	Definite	Medium high	QT, TdP	Proarrhythmia "rare."
Quinidine	Definite	High	QT, TdP	"Quinidine syncope" in 2-6% of patients.
Sotalol	Definite	High	QT, TdP	Proarrhythmia ~2%.

Drugs and thresholds

Vaughan Williams classification	Anti-arrhythmic drugs	Effect for pacing threshold
I a	quinidine	↑
	procainamide	↑~↑↑
	ajimaline	↑
	disopyramide	↑
	cibenzoline	↑↑
	pirmenol	↑~↑↑(?)
I b	aprimidine	↑
	lidocaine	→
	phenytoin	→
	mexiletine	↑
I c	propafenone	↑↑↑
	pilsicainide	↑↑↑
	flecainide	↑↑↑

C>A>B

TABLE 11-6. ANTIARRHYTHMIC DRUG EFFECT ON DEFIBRILLATOR THRESHOLD

Decrease

Dofetilide

Sotalol

N-acetylprocainamide

Variable

Procainamide

Bretylium

Propafenone

Increase

Lidocaine

Phenytoin

Flecainide

Propranolol

Mexiletine

Verapamil

Amiodarone

Quinidine

Disopyramide

Moricizine

Class 1 agents and amiodarone may significantly increase DFT.

Also Fentanyl and anaesthetic agents.

↓: decrease, →: no change, ↑: increase

Figure 1 Effects of anti-arrhythmic drugs for pacing threshold

Steroids reduce pacing threshold

Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic heart failure

Recommendations	Class ^a	Level ^b	Ref ^c
An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF $\leq 40\%$ to reduce the risk of HF hospitalization and the risk of premature death.	I	A	87–91
A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF $\leq 40\%$ to reduce the risk of HF hospitalization and the risk of premature death.	I	A	92–98

ESC Guidelines for management of acute and chronic HF 2012

Mineralocorticoid receptor antagonists:

Recommended in addition to standard therapy for patients with NYHA III-IV that spironolactone be prescribed

Eplerenone is indicated for the following:

In addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II – IV heart failure and left ventricular systolic dysfunction (LVEF $\leq 30\%$)

In addition to standard therapy in stable patients with left ventricular dysfunction (LVEF $\leq 40\%$) and clinical evidence of heart failure after recent myocardial infarction (commence within 3 -14days of MI).

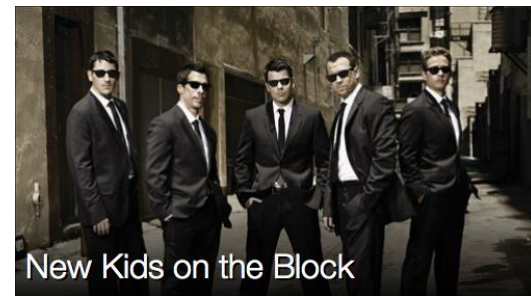
Ivabradine

- Selectively inhibits the *If* channel
- Works on the SAN (effective only in SR)
 - Ineffective in AF
- SE: bradycardia, luminous phenomenon (15%)
- Indicated for patients
 - With New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and
 - who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and
 - who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin- converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and
 - with a left ventricular ejection fraction of 35% or less.

Ivabradine

- I_f (*funny*) channel blocker
- Selectively inhibits the pacemaker I_f current (SAN)
- Slows HR
 - Ineffective in AF
 - 15% experience luminous phenomena
- **SHIFT study**
 - 26% reduction in risk of death from HF
 - 26% reduction in risk of HF hospitalisation

Sacubitril / Valsartan (Entresto)



- Paradigm HF study
 - Entresto's dual inhibition was more effective in reducing the risk of death from cardiovascular causes or hospitalization for HF than ACE inhibition with enalapril
 - The only significant side effect was symptomatic hypotension, though this did not increase the rate of discontinuation
- Indications:
 - Neprilysin inhibitor and angiotensin II receptor blocker combination to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with heart failure (NYHA Class II-IV), LVEF <35% and who are already taking stable dose of ACE-i/ ARB
- Place in therapy:

Heart failure drugs and outcomes

- Reduced mortality in treatment arm observed with
 - Ace-I
 - B-Blockers
 - Eplerenone (Emphasis/ Ephesus)
 - Spironolactone (Rales)
 - Ivabradine (SHIFT)
 - Sacubutril/valsartan (Paradigm)
- Reduced Heart failure hospitalisation
 - Digoxin



Paradigm HF

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">• Age ≥ 18 years• NYHA class II-IV• Ejection fraction $\leq 40\%$ (amended to $\leq 35\%$)• BNP > 150 pg/mL or pro-BNP ≥ 600 pg/mL• Treatment with ACE-I or ARB	<ul style="list-style-type: none">• Symptomatic hypotension• SBP < 100 mmHg• eGFR < 30 mL/min/1.73 m² or \downarrow eGFR $> 25\%$• Serum K⁺ > 5.2 mEq/L• Hx of angioedema or unacceptable side effects during receipt of ACE-I or ARB

Other drugs

RISK STRATIFICATION FOR THROMBOEMBOLISM IN ATRIAL FIBRILLATION AND ANTICOAGULATION

Risk factors, stroke risk assessment schemes, bleeding risk assessment schemes. Pharmacological and non-pharmacological methods to prevent stroke.

- NOACS and WARFARIN
 - Dabigatran/Rivaroxaban/Apixaban

Warfarin

	Condition	Points	Score	Risk
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1	0	Low
H	Hypertension : blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1		
A₂	Age ≥75 years	2		
D	Diabetes Mellitus	1	1	Moderate
S₂	Prior Stroke or TIA or thromboembolism	2		
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1		
A	Age 65–74 years	1	2 or greater	High
Sc	Sex category (i.e. female sex)	1		

Anticoagulation not required

Consider anticoagulation

Anticoagulate

Female gender scores only one point if the patient has at least one other risk factor and does not score any points in isolation.

HASBLED score

Feature	Score if present
Hypertension (Systolic ≥ 160mmHg)	1
Abnormal renal function	1
Abnormal liver function	1
Age ≥ 65 years	1
Stroke in past	1
Bleeding	1
Labile INRs	1
Taking other drugs as well	1
Alcohol intake at same time	1

Score ≥ 3 indicates increased 1 year bleeding risk= exert caution or more frequent review

Drugs interacting with warfarin

Teratogenic**

- Metabolised by the cytochrome P450 enzyme system (hepatic)
 - INR affected by drugs which induce/inhibit CYP450.

Drugs which inhibit P450 increase effects of warfarin (increase INR)

- **Omeprazole**
- **Disulfram**
- **Erythromycin**
- **Valproate**
- **Isoniazid**
- **Cimetidine, ciprofloxacin**
- **Ethanol (acute)**
- **Sulphonamides**

Drugs which induce P450 decrease effects of warfarin (lower the INR)

- **Phenytoin**
- **Carbamazepine**
- **Barbiturates**
- **Rifampicin**
- **Alcohol (chronic)**
- **Sulphonylureas**

Dronedarone- Athena trial

DESIGN

- 4628 high risk patients with paroxysmal or persistent AF or flutter randomised to dronedarone 400mg bd or placebo
 - Primary end-point was first hospitalisation due to cardiovascular events or death
 - Secondary end-points were death from any cause, death from cardiovascular causes and first hospitalisation due to cardiovascular events

ATHENA- results

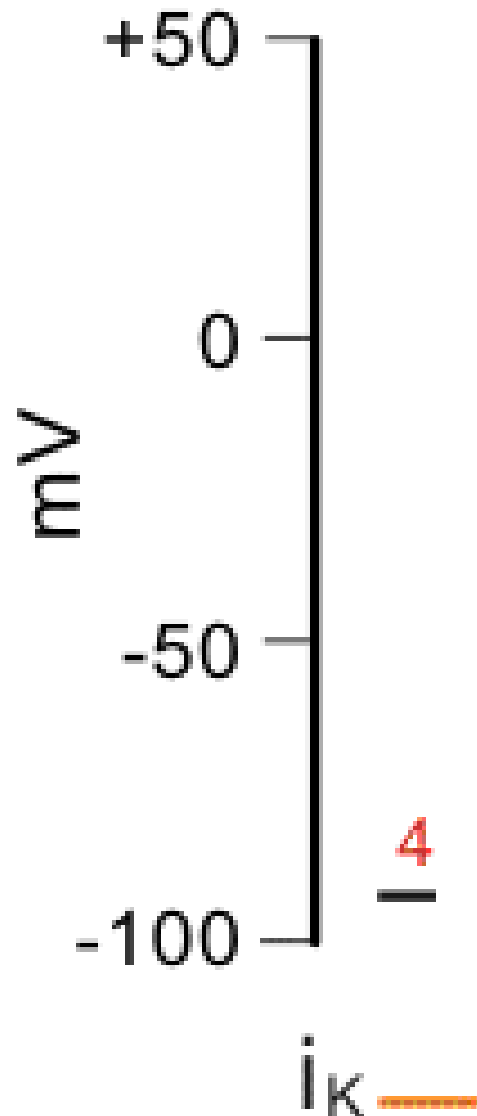
RESULTS

- Dronedarone associated with **a 24% reduction in death or cardiac hospitalisation vs placebo ($p < 0.001$)**
 - Overall mortality similar ($p = 0.18$), cardiovascular mortality lower ($p = 0.03$)
 - Higher GI side effects and increased creatinine with dronedarone; other side effects similar.

CONCLUSION

- Dronedarone reduced the incidence of hospitalisation due to cardiovascular events or death in patients with atrial fibrillation

Ventricular myocyte action potential



Pre-excited AF

Do use

- Flecainide
- Procainamide
- Propafenone
- Sotalol
- Amiodarone
- Beta blockers

Don't use

- Verapamil
- Digoxin
- Adenosine
 - These agents may enhance conduction via the accessory pathway by increasing the refractory period in the AV node
 - Digoxin may shorten the refractory period of the accessory pathway, enhancing anterograde conduction