ANTIDYSRRHYTHMICS

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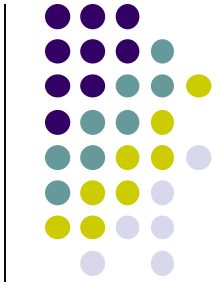
Cardiac dysrrhythmias



- **Dysrrhythmia** (arhythmia; irregular heartbeat)
  - abnormal electrical activity in the heart

- **Impulse initiation disorders**
  - **nomotopic -** abnormal SA node automaticity
  - **heterotopic -** any part of the heart initiates an impulse (without waiting for the SA node)

- **Impulse conductivity disorder**
  - **heart blocks** (AV blocks)

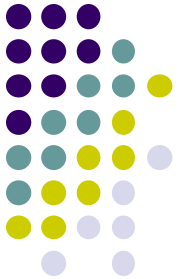
- **Etiology:**
  - **structure disorders of heart tissue –** CHF, infection
  - **extracardial –** hypokalemia, pH, thyreotoxicosis, anaemia
  - **drugs –** cardiotonics, antiarrhythmics, TCA…

Dysrrhythmias
Classification

- **By rate**
  - tachyarrhythmia
  - bradyarrhythmia
- **By mechanism**
  - automaticity
  - reentry
  - fibrillation
- **By site of origin**
  - atrial (supraventricular)
  - ventricular

www.humanillnesses.com/.../Dysrhythmia.html

ANTIDYSRRHYTHMICS



- **Common target - ion channel**

- **Specificity** - identified by targeting particular type of ion channel

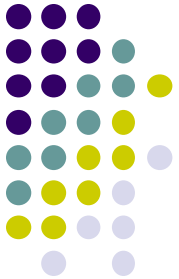
- **The same reason**

  (targeting particular type of ion channel)

  can result in significant

  prodysrrhythmogenic effects

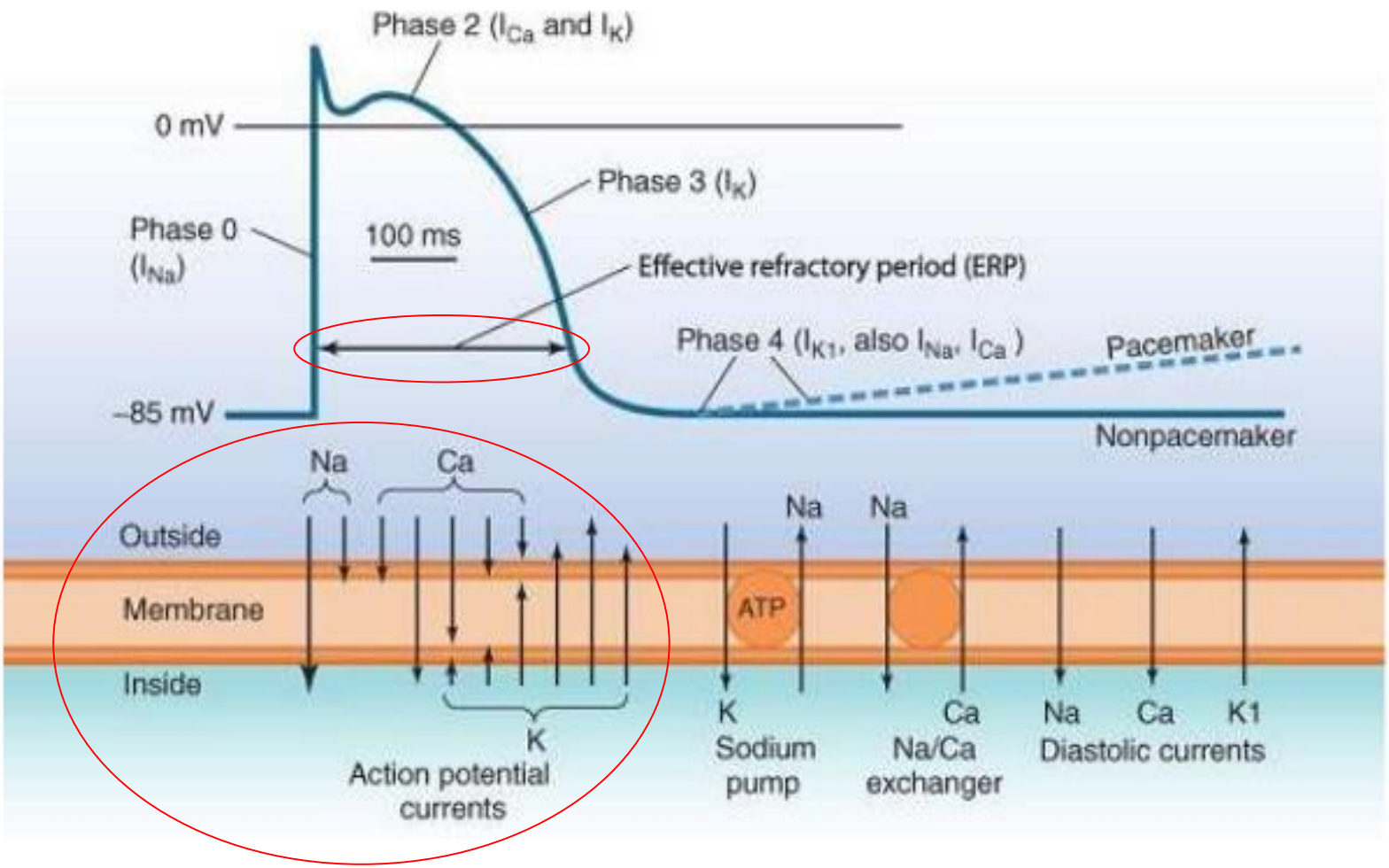
Antidysrrhythmics
Classification



- **Vaughan – Williams -** according to their general effect
- Useful in clinical cardiology ???
- **4 big classes of antidysrrhythmics**

- **Class I – Na^+ channel blockers**
- **Class II – β – blockers**
- **Class III – K^+ channel blockers**
- **Class IV – Ca^{2+} channel blockers**

NORMAL CARDIAC AP



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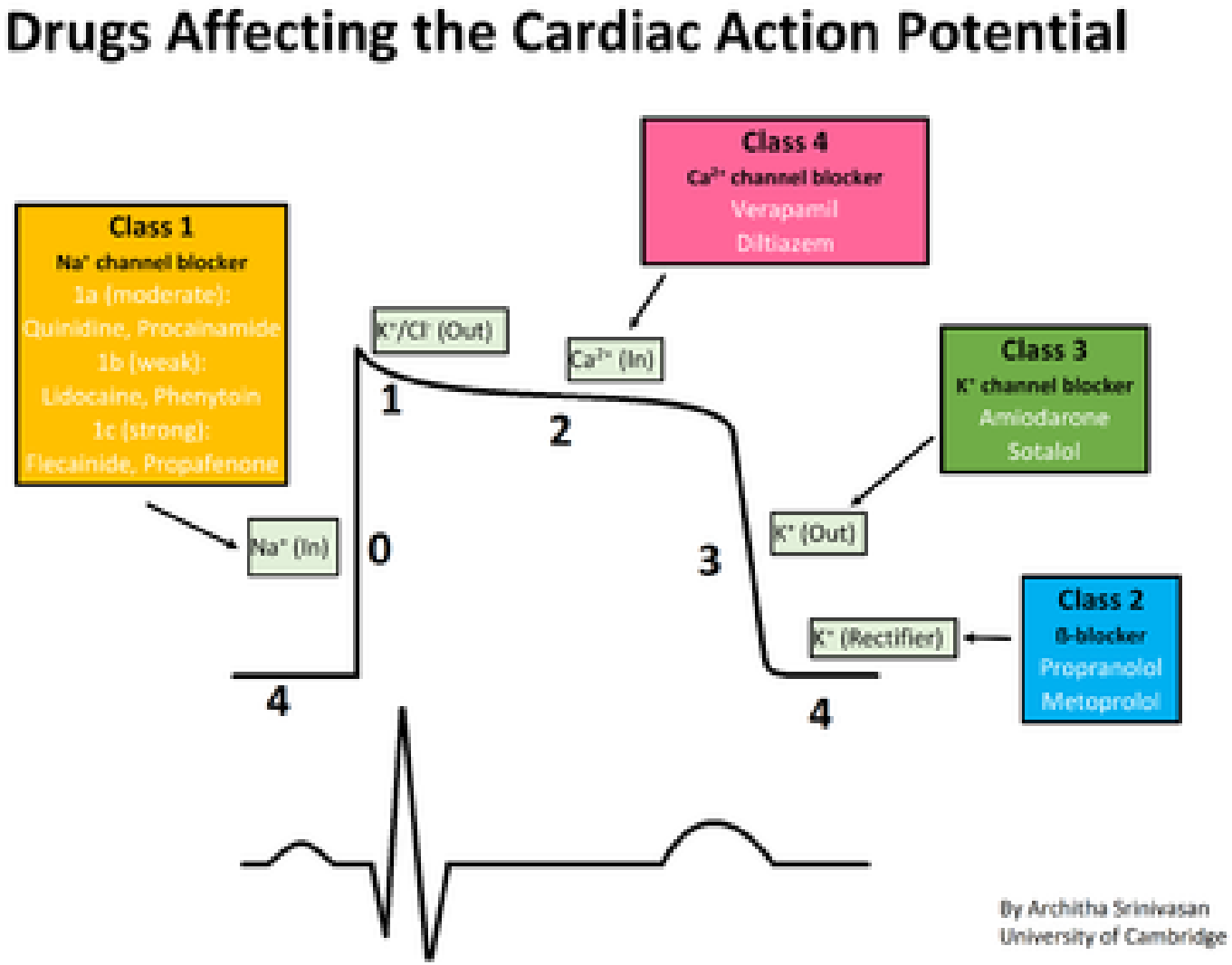
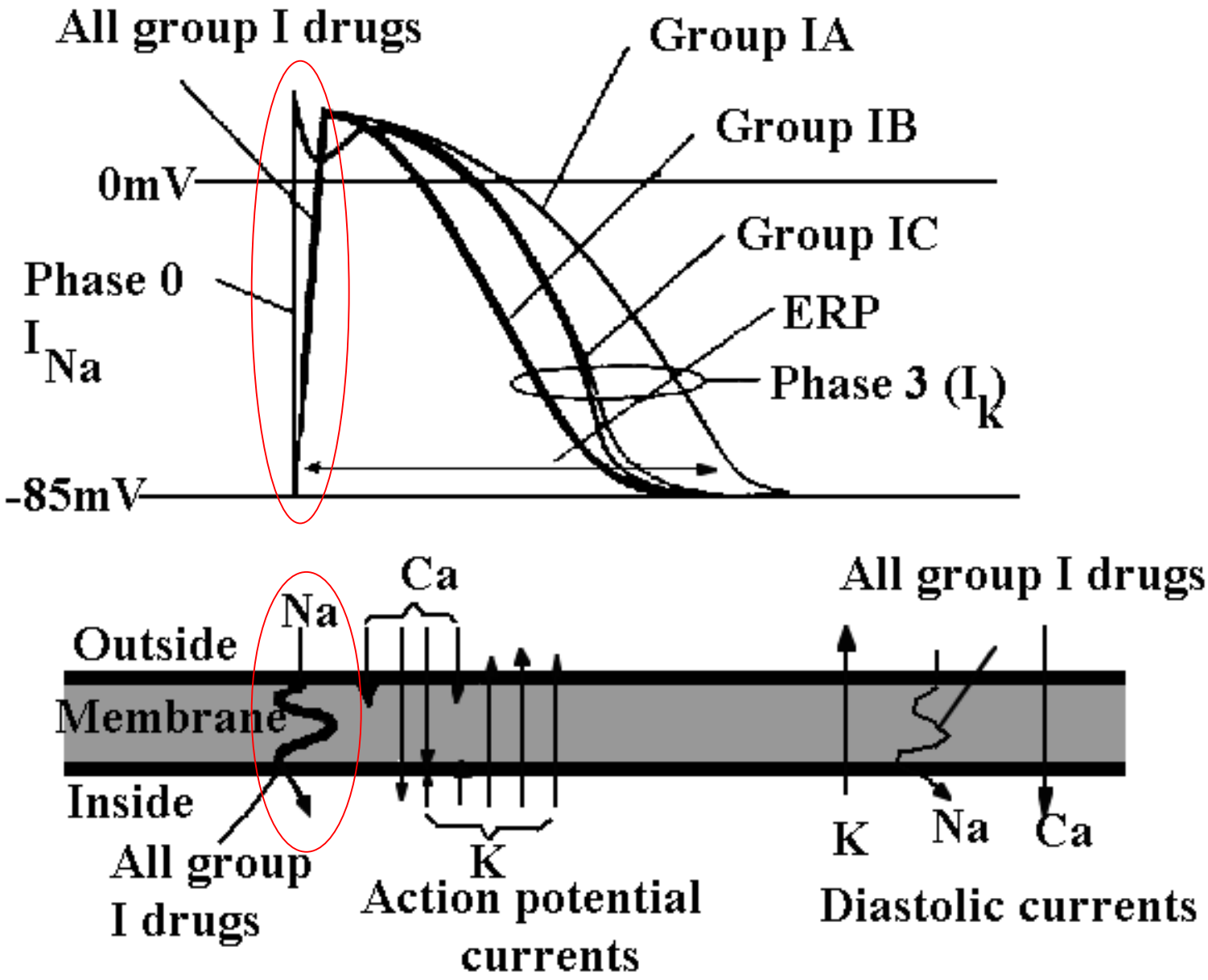
General effects of different classes of antiarrhythmics



Class I

IA	**Moderate** depression of phase-0 retardation of conduction prolongation of repolarization	*procainamide* *quinidine* *disopyramide* *ajmaline* *prajmaline*
IB	**Weaker** depression of phase-0 retardation of conduction & shortening of repolarization selectively in abnormal/ischemic tissue	*lidocaine* *mexiletine* *tocainide* *aprindine*
IC	**Significant** depression of phase-0 ↓↓↓ retardation of conduction ± effect on repolarization (minimal)	***propafenone*** ***flecainide*** *encainide*



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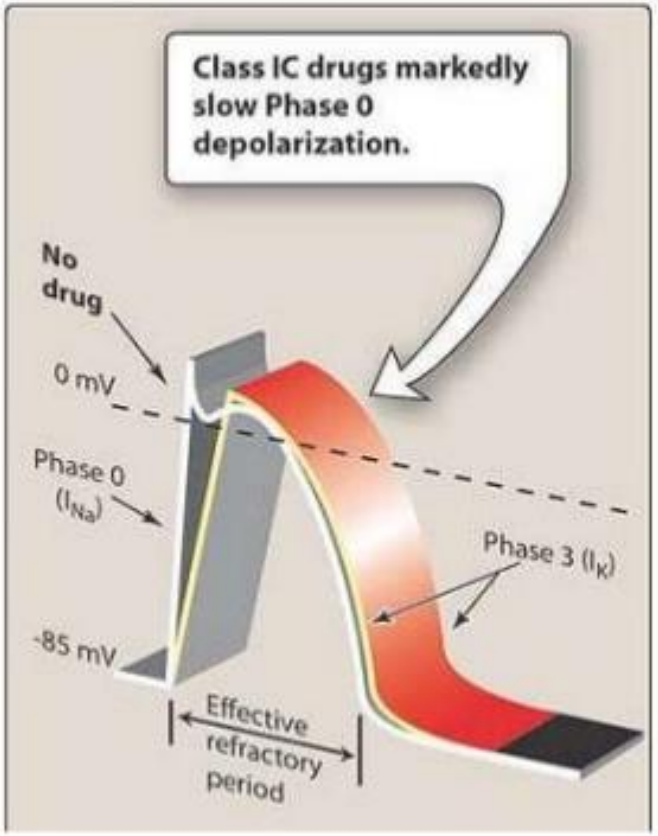
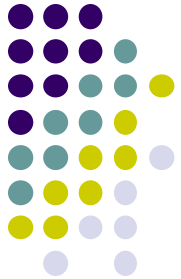
Class IC

Have minimal effect on repolarization
Are most potent sodium channel blockers

- Risk of cardiac arrest , sudden death so not used commonly
- May be used in severe ventricular arrhythmias



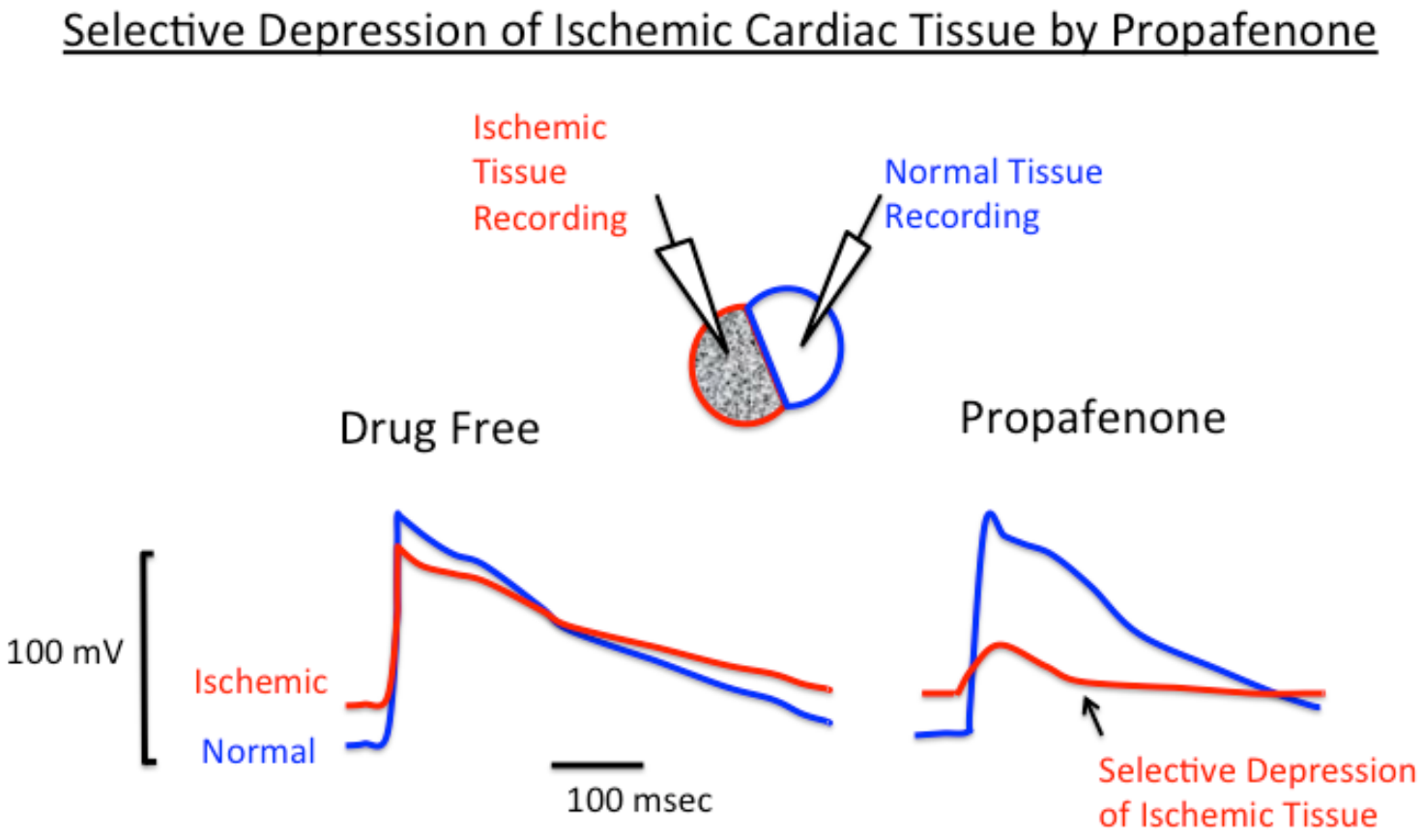
Propafenone
MOA



Class IC antidysrrhythmic drug

- Direct **stabilizing action** on myocardial membranes
- **β-sympatholytic activity** (at about 1/50 the potency of *propranolol*)
- Reduction of upstroke velocity (phase 0) of the monophasic action potential
- Reduction of fast inward current carried by Na^+ ions (in Purkinje fibers, & to a lesser extent myocardial fibers)
- **Local anaesthetic** effects (approximately equal to *procaine*)

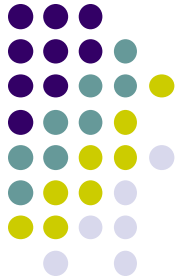
Propafenone
In cardiac ischemia



Adapted from Zeiler et al, 1984

Propafenone

Effects & indications



Effects:

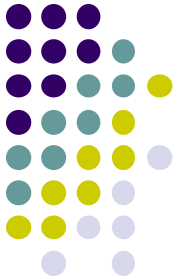
- ⇑ diastolic excitability threshold
- Minimal effect on repolarization
- Reduces spontaneous automaticity
- Depresses triggered activity
- Exerts a **negative inotropic effect** on the myocardium

Indications:

- **Paroxysmal or persistent atrial fibrillation/flutter** (AF)
- **Paroxysmal supraventricular tachycardia** (PSVT)

  (both associated with disabling symptoms)
- **Ventricular dysrrhythmias** (sustained ventricular tachycardia) that, in the judgement of the physician, are life-threatening

Propafenone
PK

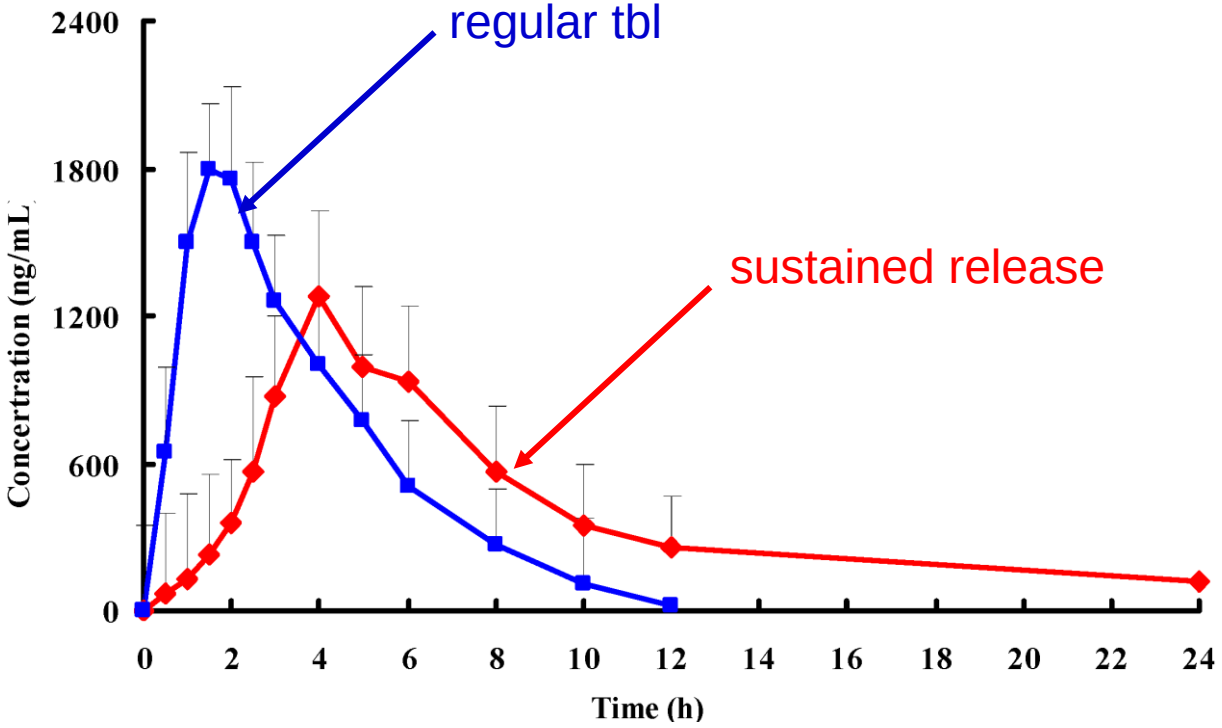


- Nearly completely absorbed (peak ≈ 3.5 h)
- **Extensive** saturable **first pass effect**
- Very high degree of **interindividual variability**
- Two genetically determined patterns of metabolism:
  - extensive metabolizers – 90% (elimination t½ from 2 to 10 h)
  - slower metabolizers – 10% (elimination t½ from 10 to 32 h)
- Severe liver dysfunction ⇑ the bioavailability

- **Drug should be titrated carefully with close attention paid to clinical & ECG evidence of toxicity**

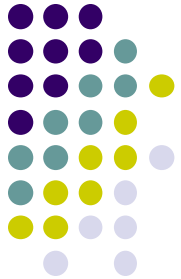
Propafenone
Extended-release capsules

- Extended-release capsules - to prolong the time to recurrence of symptomatic AF in patients with episodic AF (paroxysmal or persistent) who do not have structural heart disease



Propafenone

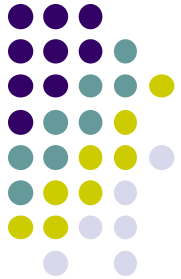
SE



- **May cause new or worsened dysrrhythmias**
- Slows AV conduction & also causes first degree AV block
- Congestive heart failure (both β-blockade & a dose-related negative inotropic effect)

- Hypersensitivity reactions, lupus-like syndrome
- Agranulocytosis
- CNS disturbances (dizziness, lightheadedness)
- Gastrointestinal upset (metallic taste)
- Nonallergic bronchospasm

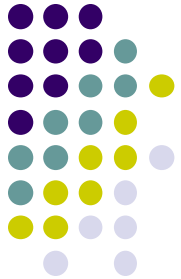
Flecainide
PK & SE



Class IC antidysrrhythmic drug

- Structurally similar to ***propafenone***
- Does **not** undergo **first-pass effect**
- **About 30%** of a single oral dose is excreted in **urine as unchanged drug**
- **Two metabolites** (primarily conjugated) account for most of the remaining portion of the dose
- Can cause new or worsened **supraventricular or ventricular dysrrhythmias**
- Has a **negative inotropic effect** & may cause or worsen CHF

Flecainide
Indications



- Paroxysmal **supraventricular tachycardias** (including atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia & other supraventricular tachycardias of unspecified mechanism)
- **Paroxysmal atrial fibrillation/flutter**

  (both associated with disabling symptoms)
- Prevention of documented **ventricular dysrrhythmias**

  (that in the judgment of the physician are life-threatening)

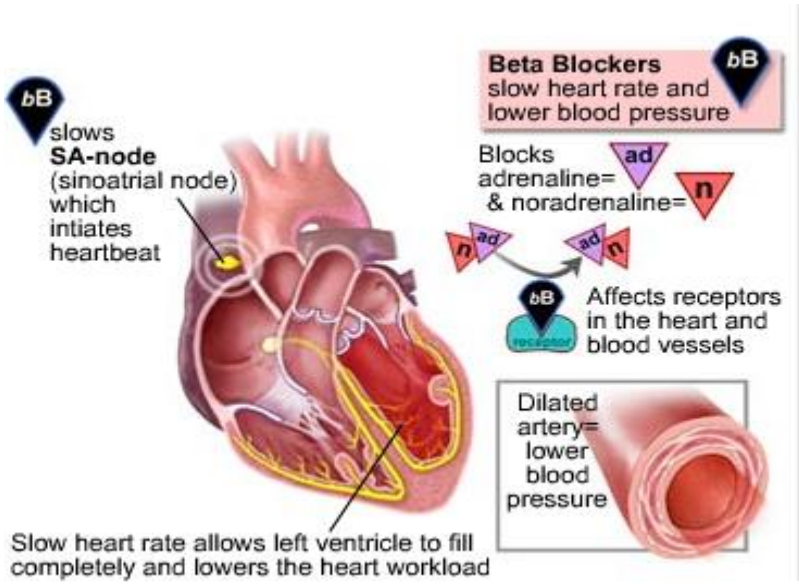
Classes II, III, IV

Class	Mechanism	Drug
II	β-blockers	*Atenolol* ® *Bisoprolol* ® *Carvedilol* ® *Metoprolol* ® *Nebivolol* ® *Propranolol* ®.....
III	K^+ channel blockers	*Amiodarone* ® *Dronedarone* ® *Sotalol* *Bretylium*
IV	Ca^+ channel blockers	*Verapamil* ® *Dilthiazem* ®

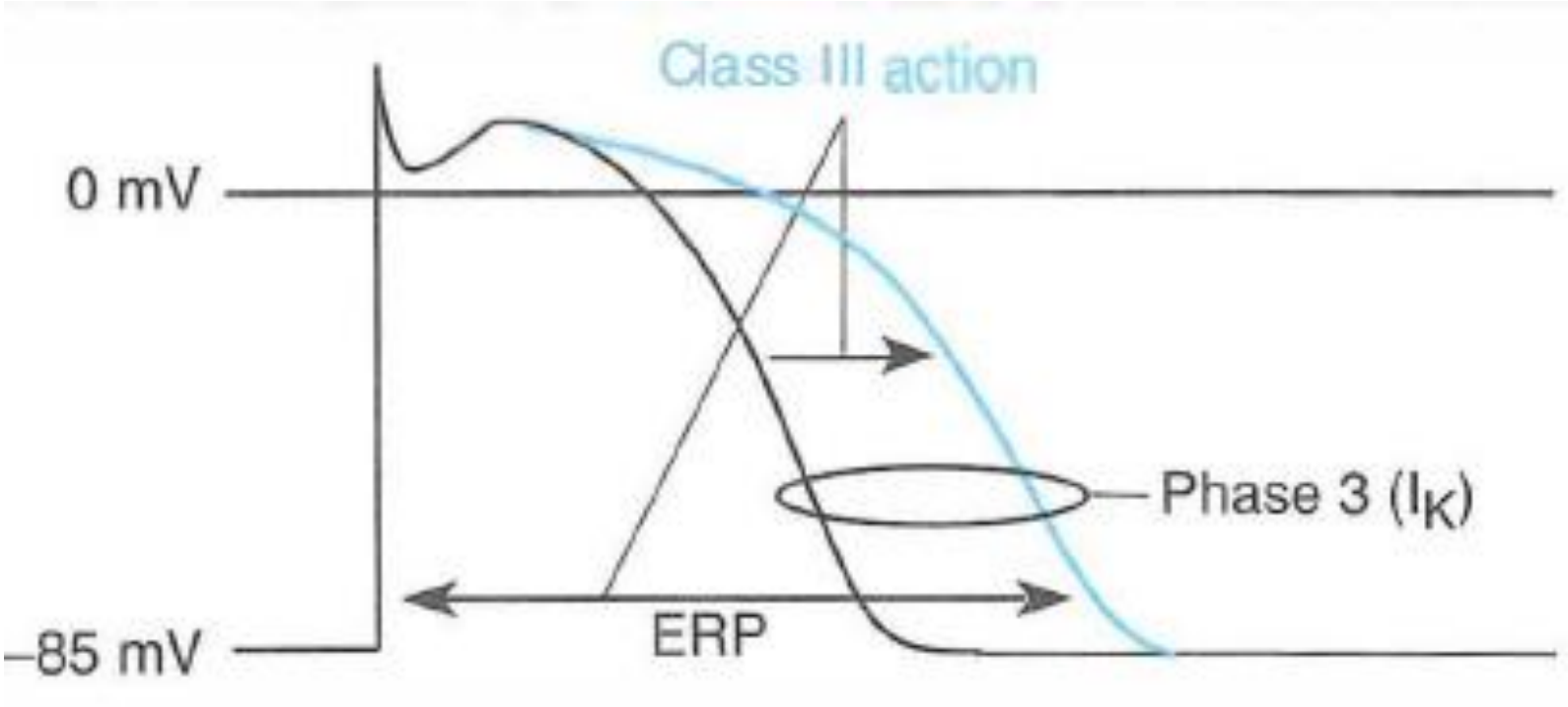
Class II: Beta blockers

- β-receptor stimulation:
  - ↑ automaticity,
  - ↑ AV conduction velocity,
  - ↓ refractory period
- β-adrenergic blockers competitively block catecholamine induced stimulation of cardiac β- receptors

- ⇓ slope of phase 4 (all of them)

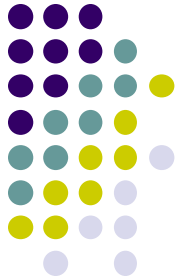


Class III



- Block of repolarizing K^+ channels
- Prolong phase 3
- Prolonged repolarization & ERP

Amiodarone
MOA



Drug with predominantly class III effects

- **Prolongs** the myocardial cell-**action potential duration** & ERP
- Noncompetitively ⇓ **α- & β-adrenergic** receptors
- By ⇑ the ERP, they are very useful in suppressing tachydysrrhythmias caused by **reentry mechanisms**
  (reentry occurs when an action potential reemerges into normal tissue when that tissue is no longer refractory)

These electrophysiologic effects are reflected in cardial effects

Amiodarone

Effects & indications

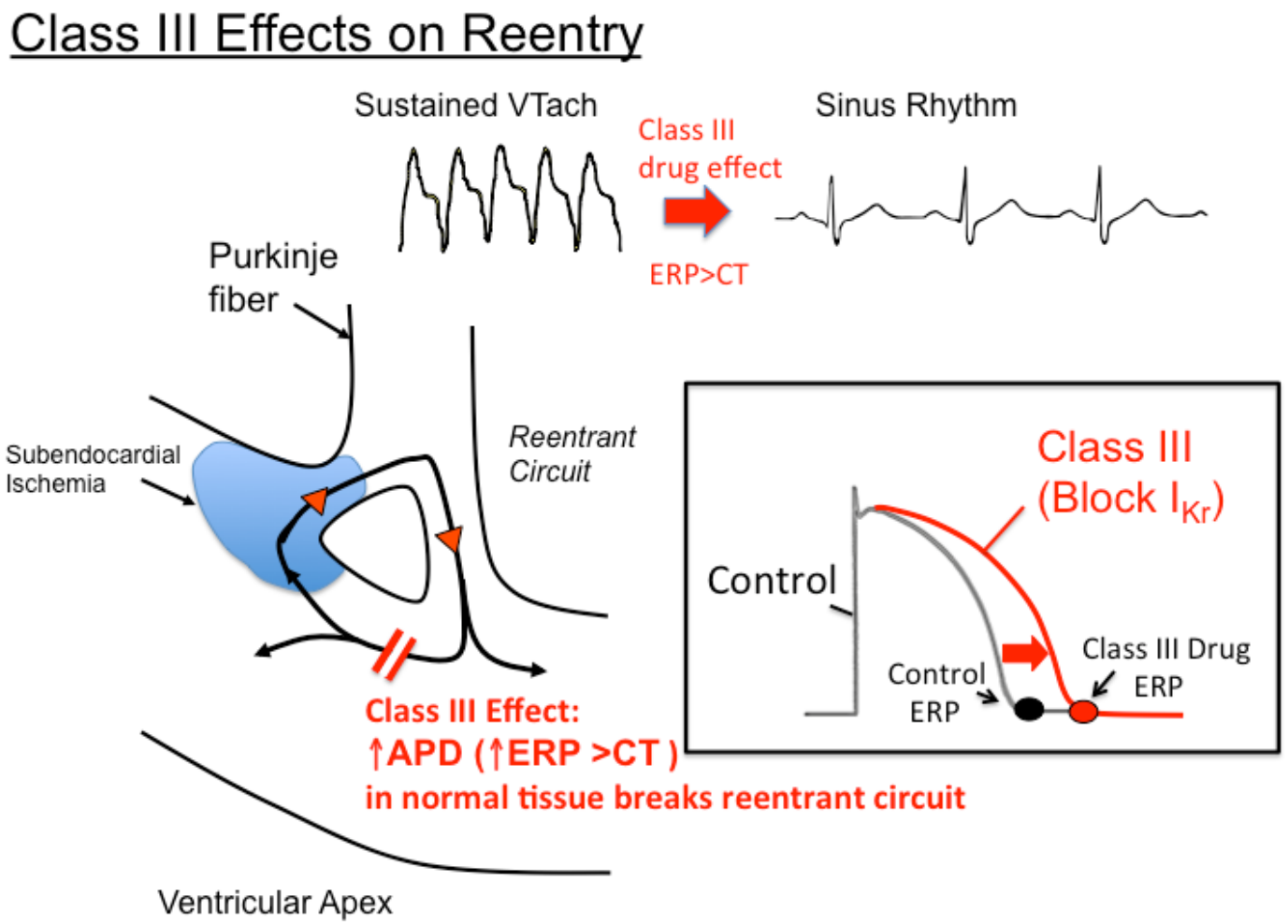
Effects:

- ⇓ sinus rate of 15 to 20%
- ⇑ PR & QT intervals of about 10%
- development of U-waves
- changes in T-wave contour

Indications:

- Because of its **life-threatening SE,** *amiodarone* is indicated only for the treatment of the following documented dysrrhythmias, not responding to adequate doses of other available antiarrhythmics:
  - **recurrent ventricular fibrillation**
  - **recurrent haemodynamically unstable ventricular tachycardia (reentry mechanism** - is due to the electric signal not completing the normal circuit, but rather an alternative circuit looping back upon itself = there develops a self-perpetuating rapid & abnormal activation - „circus movement")

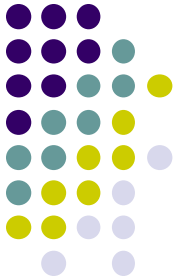
Amiodarone in reentry



APD - atrial premature depolarization
ERP – effective refractory period
CT - conduction time

Amiodarone

PK



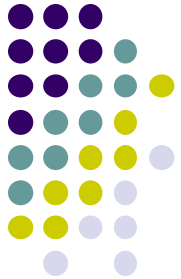
- Slowly & variably absorbed (peak ≈ 3 to 7 h)
- Onset of action may occur in 2 to 3 days
- Considerable **individual variability**
- Eliminated primarily by hepatic metabolism & biliary excretion
- **No dosage adjustment** in **renal, hepatic, or cardiac** abnormalities
- However, close clinical monitoring is prudent for **elderly patients** & those with **severe left ventricular dysfunction** (during chronic treatment)
- Slow rate of elimination → **antidysrrhythmic effects persist for weeks or months** after discontinuation

Amiodarone

SE

- The use of ***amiodarone*** is limited by toxicity due its **high iodine content,** resulting in:
  - **pulmonary toxicity** (pulmonary fibrosis, hypersensitivity or interstitial/alveolar pneumonitis – 10 to 17%)
  - **thyroid disease**
- Other serious SE include:
  - **dysrrhythmia** (making the arrhythmia less well tolerated or more difficult to reverse - 2 to 5%)
  - **liver injury** → usually mild (fatal in few cases)
- It possesses **major management problems:**
  - patients with the indicated arrhythmias must be hospitalized while the loading dose of *amiodarone* is given (a response generally requires at least 1 week, usually 2 or more)

Sotalol
General



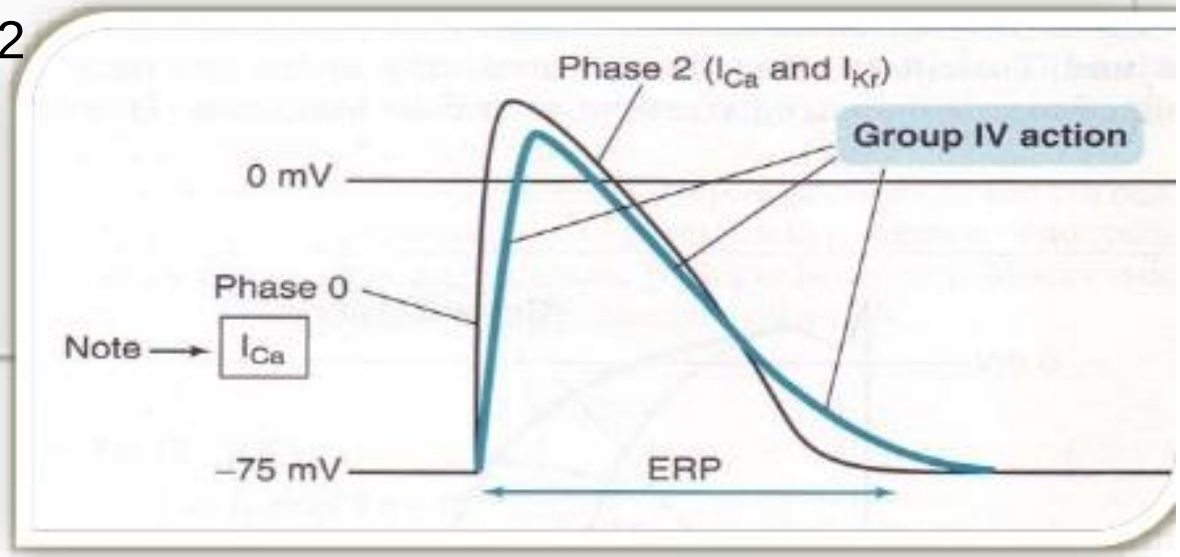
Drug with the properties of:

- **Class II – *l-sotalol*** (β-adrenoreceptor blocking) &
- **Class III – *d-sotalol*** (cardiac action potential duration prolongation)

- It is **not metabolized** & it is **excreted** via the **kidney** in the unchanged form (no drug interactions associated with hepatic metabolism)
- Treatment of documented **ventricular dysrrhythmias** (such as sustained ventricular tachycardia) that in the judgment of the physician are life-threatening
- Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/flutter)

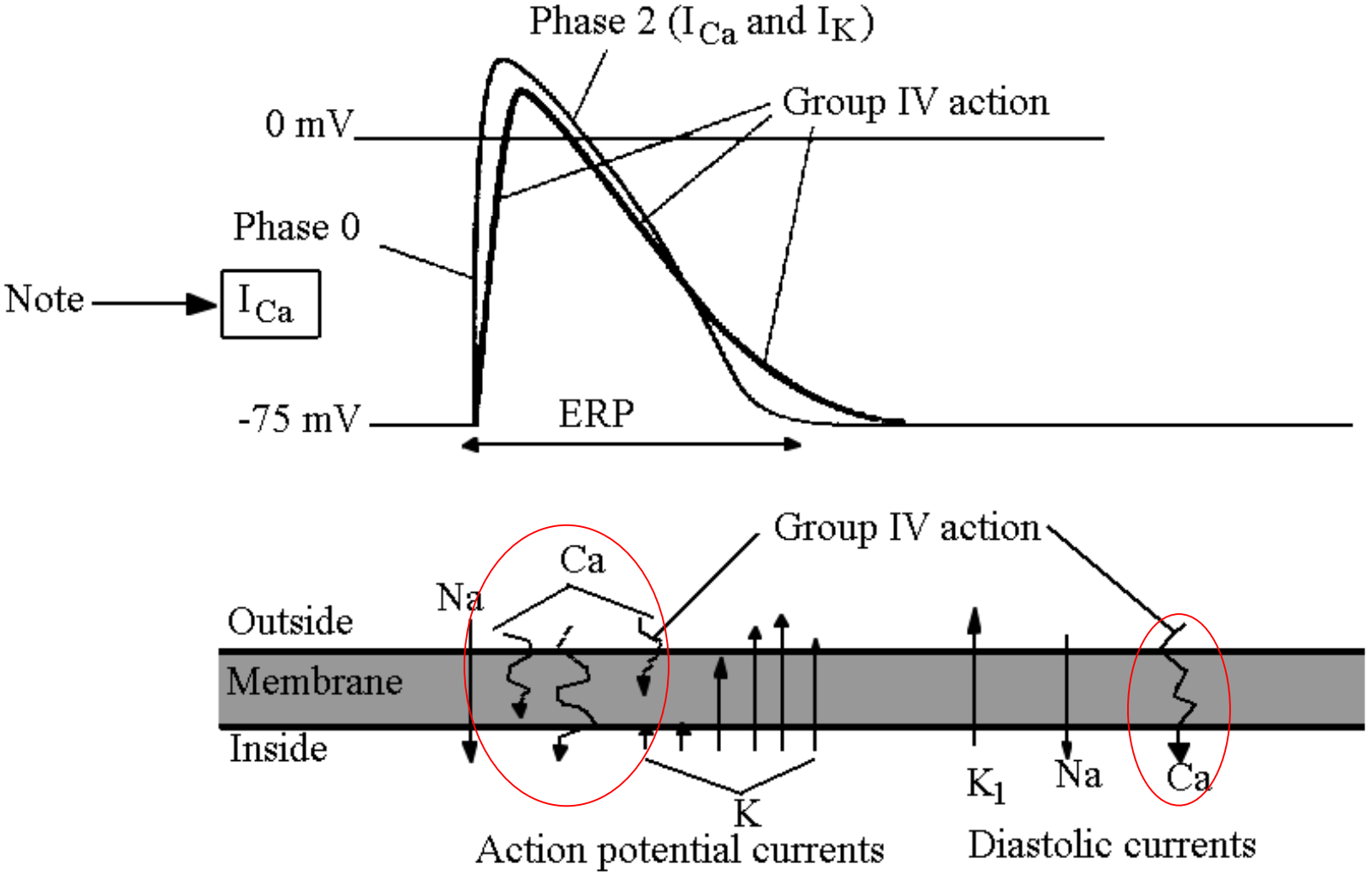
Class IV – Verapamil, Diltiazem

- **Mechanism**-block L-type calcium channels.
  - ↓ Rate of phase 4 in SA / AV node
  - Slow conduction – prolong ERP
  - Phase 0 upstroke ↓
  - prolong phase 2



ERP – effective refractory period

Verapamil & dilthiazem



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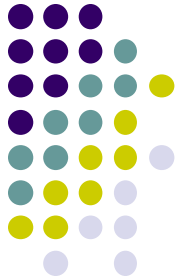
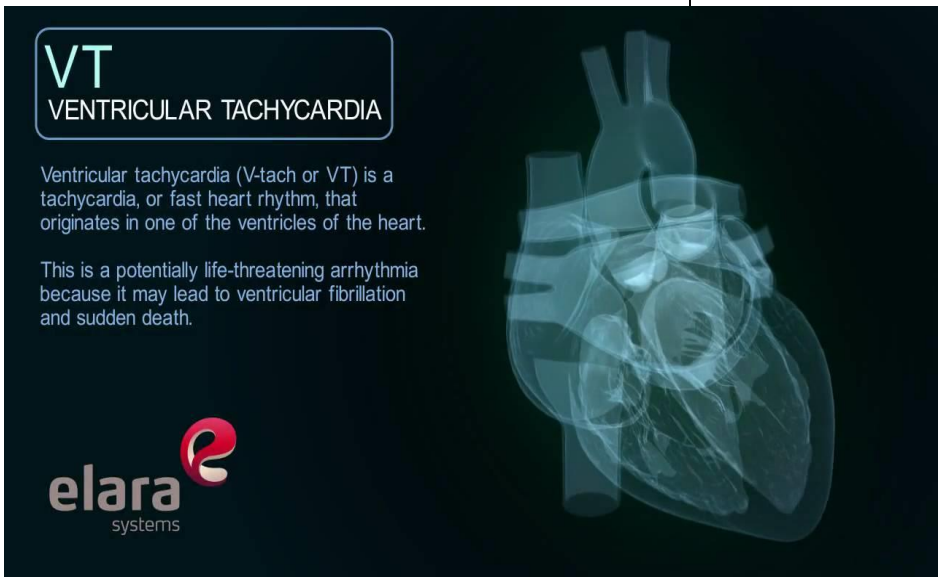
Verapamil
Effects & indications

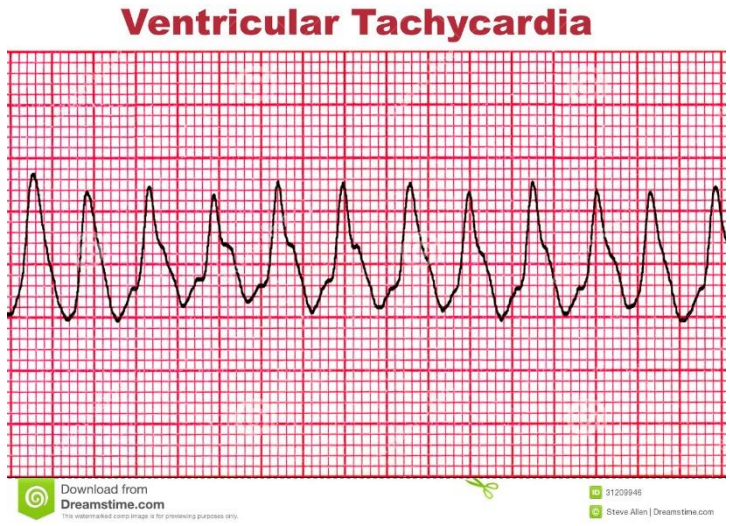


- ***Verapamil*** remains the most widely used CCB for the treatment of cardiac dysrrhythmias
- It is the most potent & effective drug for the acute treatment of paroxysmal supraventricular tachycardia particularly, circus movement tachycardia
- As a powerful depressant of atrioventricular nodal conduction it ⇓ the ventricular rate in atrial flutter & fibrillation with reversion to sinus rhythm
- It is also effective in supraventricular tachydysrrhythmias following open-heart surgery & MI

Verapamil
Contraindications

- It is **not an effective drug** against ventricular dysrrhythmias unless due to coronary artery spasm
- The use of *verapamil* should be avoided in the presence of sick sinus node syndrome, clinical cardiac failure & treatment with other negative inotropic drugs

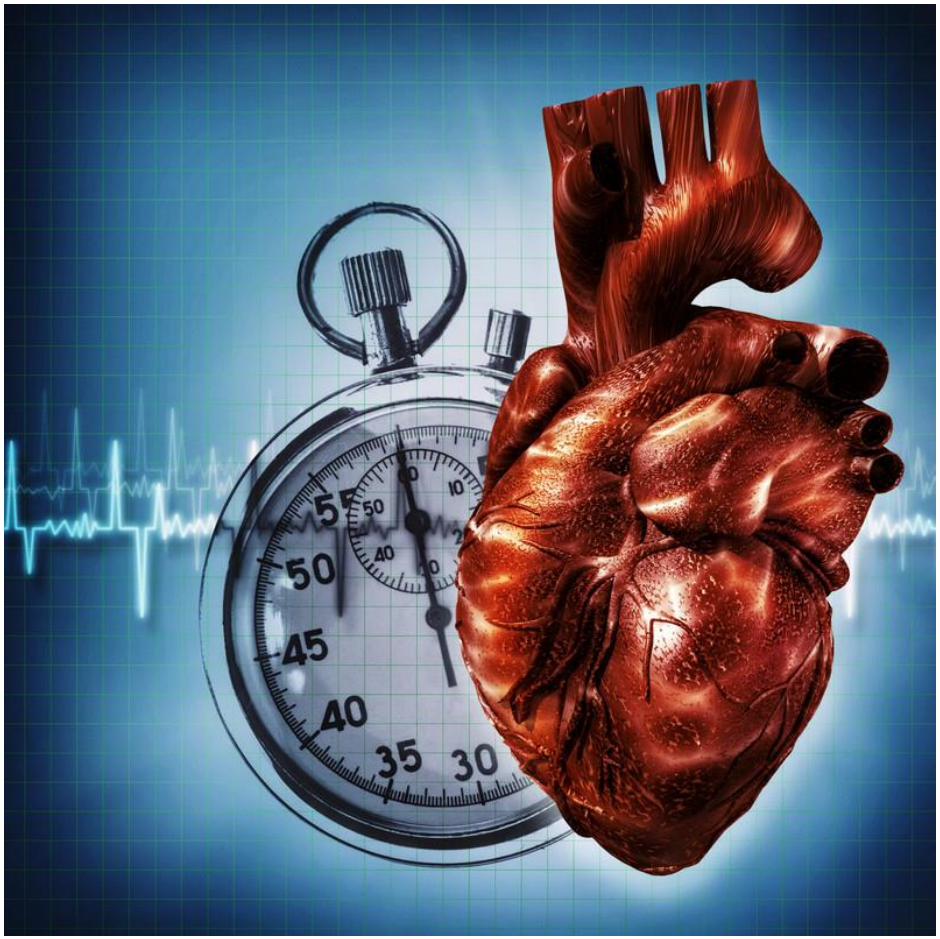




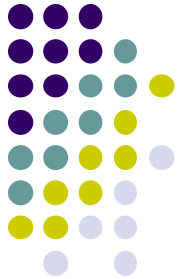
Other antidysrrhythmics

Variable mechanism

- *Digoxin*
- *Magnesium sulfate*
- *Adenosine*



Other antidysrrhythmics



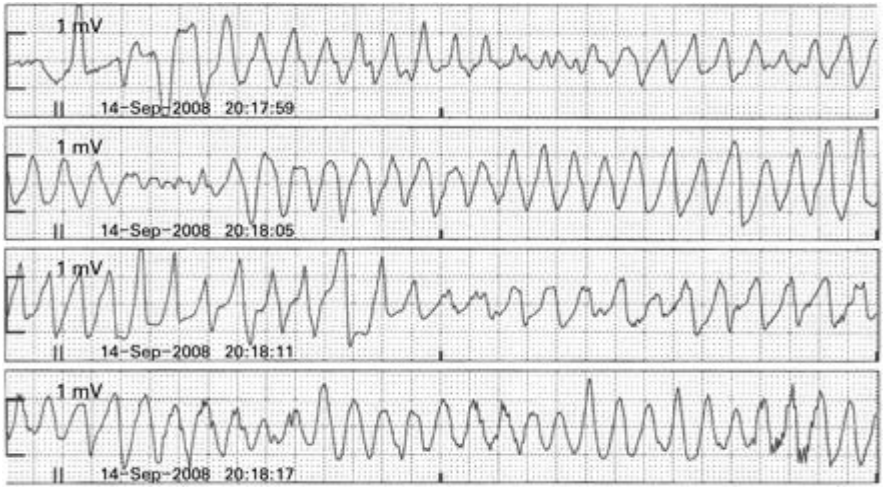
- **Digitalis glycosides – cardioglycosides *(digoxin)***
  - **negative dromotropic effect – vagus n. stimulation →**
    (prolong AV conduction & propagation in His bundle - prolong PQ interval)
    control the action of ventricles in atrial fibrillation
  - **indication: atrial fibrillation & flutter**

- **Magnesium, potassium – in tachydysrrhythmia induced by digitalis cardioglycosides, other drugs or situations** (torsades des pointes)
  - significance of hypokalemia & hypomagnesemia in *digoxin* intoxication

Torsades des pointes

- **Polymorphic ventricular tachycardia:**
  - associated with long QT syndrome
  - **can degenerate into ventricular fibrillation**
- **Causes:**
  - diarrhea, hypokalemia, hypomagnesemia
  - drug interactions (metabolism of drugs causing QT elongation - *amiodarone, methadone, erythromycin, citalopram, phenothiazines, sotalol, ondasetron* …

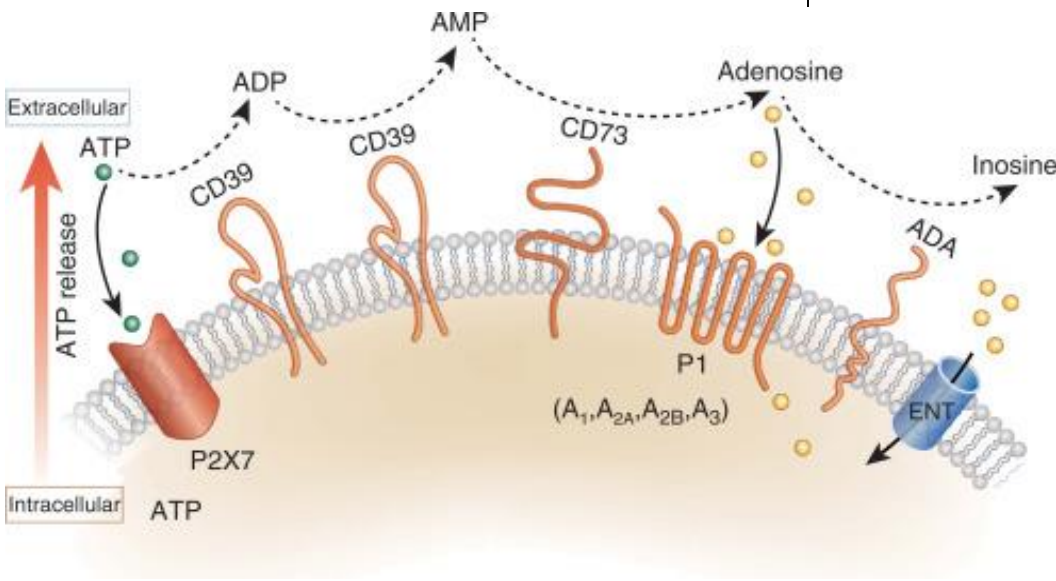
Rhythm strips demonstrating torsades de pointes



- **Therapy:**
  - ***magnesium sulfate***
  - antiarrhythmics *(β-blockers)*
  - pacing the heart to ⇓ the action potential duration

Adenosine

- Endogenous purine nucleotide:
  - binds to **A_1-receptors**
  - in structures of slow response it **blocks entry of Ca^{2+}** in the cells → ⇓ stimuly in SA node
  - ⇓ of conduction in AV node



PK:

- extremely short $t_{1/2}$ < 10 sec. (i.v.)
- fast & effective (90 - 95% cases) management of **AV nodal „reentry“ tachycardias**

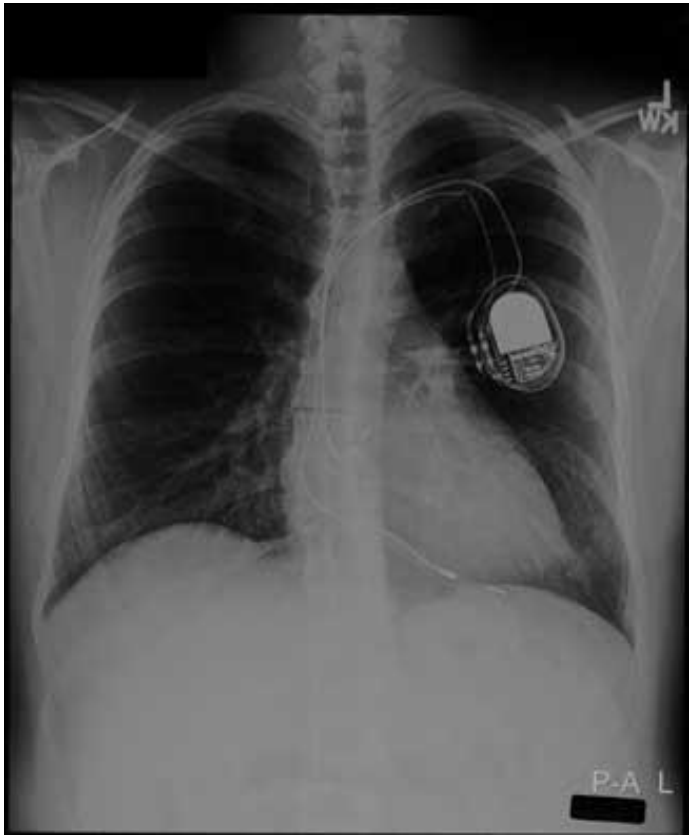
SE:

- headache, dyspnea, chest pressure, bronchial asthma

Drugs influencing bradydysrhythmias

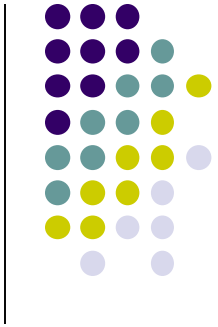
- **Parasympaticolytics**
  atropine

- **β_1- sympaticomimetics**
  isoprenaline



- **Cardiostimulation**

Summary



- There are 4 extensively used antidysrrhythmics in treatment of tachydysrrhythmias:
  - ***propafenone***
  - ***amiodarone***
  - ***β-blockers***
  - ***verapamil***

- The other drugs previously used were almost abandoned for their antidysrrhythmic indication mainly for:
  - high danger of serious adverse reactions