Agents used in HT, CHF, Dysrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>HF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers (BBs)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>HF (CI: unstable HF, broncho-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>spasm, significant bradycardia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>depression); Raynaud D. Caution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in diabetes, asthma (use gl−)</td>
</tr>
<tr>
<td>Cα++-Channel blockers (CCBs)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>HF, cardiac depression,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>constipation, gingival hyperplasia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>edema, reflex tachycardia</td>
</tr>
<tr>
<td>ACEI / ARBs /</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Angioedema, hyperkalemia, cough-</td>
</tr>
<tr>
<td>Aliskiren</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-pain, hypotension, glucose, taste</td>
</tr>
<tr>
<td>Diuretics (Thiazides)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>GFR &gt;30, hypokalemia (CG), Ti&lt;1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diabetes, [glucose tolerance]</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Many Rx interactions, [K+], Lose</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF important, low K+ = Fluidity,</td>
</tr>
<tr>
<td>Vasoconstrictors</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>flushing, dizziness, headache,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nausea, reflex tachycardia</td>
</tr>
<tr>
<td>Nα+-Channel blockers</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Effects enhanced in depolarized,</td>
</tr>
<tr>
<td>Nitrates</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>damaged tissue, Phase 5, i-CV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NOxGMP, tolerance (off-periods),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>flushing, dizziness, headache,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>

Heart Physiology

P - atria depolarization
QRS - ventricle depolarization
PR - conduction A-V
T - ventricle repolarization
QT - duration ventricle repolarization

Heart Physiology

Closed system
Pressure driven
Supply nutrients/O2
Remove metabolites

P - atria depol.
QRS - ventricle depol.
PR - conduction A-V
T - ventricle repol.
QT - duration
ventricle repolarization

Review of Physiology

- The response of excitable cells to electrical stimulation is a function of # of available Na channels (an index is dV/dt or Phase 0)
- Steady membrane depolarization decreases Na current, dV/dt and conduction velocity
- Abnormal heart tissue is usually depolarized
- Na channel availability results from Na channels being in different states……
Effect of drugs on number channels available and recovery time constant...depends on the resting membrane potential

What this means:
1. Conduction in damaged/abnormal heart tissue is decreased
2. Antidysrhythmics will work better on Na channels in depolarized cells, and slow their recovery from excitation

1. Characteristics:
   a. flutter – very rapid but regular depolarization
   b. tachycardia – increased rate
   c. bradycardia – decreased rate
   d. fibrillation – disorganized depolarization activity

2. Sites involved:
   a. ventricular
   b. atrial
   c. sinus
   d. AV node
   e. supraventricular (SVT, atrial myocardium or AV node)

Classification of dysrhythmias

Characteristics of Dysrhythmias

Definitions:
- normal sinus rhythm (60-100bpm), SA node pacemaker
- arrhythmia; any abnormality of firing rate, regularity or site of origin of cardiac impulse or disturbance of conduction that alters the normal sequence of activity of atria and ventricles.

Occurrence:
- 80% of patients with acute myocardial infarctions
- 50% of anaesthetized patients
- about 25% of patients on digitalis

Cardiac Action Potentials

Ion Permeability

<table>
<thead>
<tr>
<th>Ion</th>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>In</td>
<td></td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
<tr>
<td>Out</td>
<td></td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ion</th>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
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<tr>
<td>Out</td>
<td></td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Na⁺/Ca²⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)
Mechanisms of dysrhythmias

1. Abnormal impulse generation (abnormal automaticity)
   a. automaticity of normally automatic cells (SA, AV, His)
   b. generation of impulses in normally non-automatic cells
      - development of phase 4 depolarization in normally non-automatic cells
      - 'triggered activity' due to afterdepolarizations
      - early afterdepolarization
      - delayed afterdepolarization

2. Abnormal impulse conduction (more common mechanism)
   a. AV block – ventricle free to start own pacemaker rhythm
   b. Re-entry: re-excitation around a conducting loop, which produces tachycardia
      - unidirectional conduction block
      - establishment of new loop of excitation
      - conduction time that outlasts refractory period

Strategies of Antidysrhythmic Agents

Suppression of dysrhythmias

A. Alter automaticity
   i. decrease slope of Phase 4 depolarization
   ii. increase the threshold potential
   iii. decrease resting (maximum diastolic) potential

B. Alter conduction velocity
   i. mainly via decrease rate of rise of Phase 0 upstroke
   ii. decrease Phase 4 slope
   iii. decrease membrane resting potential and responsiveness

C. Alter the refractory period
   i. increase Phase 2 plateau
   ii. increase Phase 3 repolarization
   iii. increase action potential duration

Abnormal impulse generation: ‘triggered activity’:
EADs and DADs

Early Afterdepolarizations

Delayed Afterdepolarizations

Unidirectional Block

Damaged tissue is usually depolarized → ↓ conduction velocity

Classification of Antidysrhythmic Drugs

Vaughan-Williams classification (1970), subsequently modified by Harrison.

Helpful, But?

1. based on electrophysiological actions in normal tissue
2. presumes a mechanism of action of antidysrhythmic drugs
3. consists of four main classes and three subclasses
4. does not include actions of other agents (ie. adenosine)

Vaughan-Williams Classification

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Mechanism</th>
<th>Prototype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.A.</td>
<td>Moderate Na block Ph.0; slow conduction; ↑ APD</td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procainamide</td>
</tr>
<tr>
<td>I.B.</td>
<td>Minimal Na block Ph.0; slow conduction (less); shortened Ph.3 repolarization</td>
<td>Lidocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td>I.C.</td>
<td>Marked Na block Ph.0; slow conduction; no change APD or repolarization. Increased suppression of Na channels</td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Encainide</td>
</tr>
<tr>
<td>Class II</td>
<td>Beta blockers; decrease adrenergic input. No major effect on APD, suppress Ph.4 depolarization</td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>others</td>
</tr>
<tr>
<td>Class III</td>
<td>Prolong repolarization/refractory period other means than exclusively Na block (mainly K+ channel blockade).</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ibutilide</td>
</tr>
<tr>
<td>Class IV</td>
<td>Ca channel blockers. Slow conduction and ↑ effective refractory period in normal tissue (A-V node) and Ca-dependent slow responses of depolarized tissue (atria, ventricle, Purkinje)</td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diltazem</td>
</tr>
<tr>
<td>Others</td>
<td>Adenosine, Digoxin, Anticoagulants, ANS agents</td>
<td></td>
</tr>
</tbody>
</table>
Shortcomings: Vaughan-Williams system (V-W)

1. Based on response in normal tissue, not damaged.
   Hybrid: Class I, III & IV agents block ion channels, Class II block receptors.
2. Incomplete: eg. adenosine, digitalis, cholinergic agonists, alpha adrenergic blockers or agents that modulate gap junctions, ion pumps or exchangers. Also ignores drug metabolites.
4. Describes drugs that block ion channels/receptors and does not consider drugs that activate channels or receptors.
5. Does not incorporate variable mode of action: slowing tachycardias, terminating dysrhythmias, or preventing them.
**Na Channel States**

Quinidine 1A: Open
Lidocaine 1B: Open & Inactive

In depolarized tissue

---

**Key Aspects of Drug Action and Therapy...**

**D.** Drugs affect different parts of the heart: Beta-blockers and CCBs used for SVT

1. Ca channel blockers (Class IV) are selective for A-V and S-A nodes, where Ca action potentials predominate.

2. Lidocaine (Class IB) has been useful for treating PVCs in Purkinje fibers, since longer APDs in Purkinje yield more inactivated Na channels. Lidocaine selectively blocks inactivated state and some open Na channels. Lidocaine has little effect, in contrast, on atrial tissue.

3. Quinidine affects both atrial and ventricular dysrhythmias (but has been mostly used to treat atrial fibrillation).

---

**Quinidine (Class IA prototype)**

Other examples: Procainamide, Disopyrimide

1. General properties:
   a. D-isomer of quinine
   b. As with most of the Class I agents
      - moderate block of sodium channels
      - decreases automaticity of pacemaker cells
      - increases effective refractory period/AP duration

---

**Actions of Quinidine**

Cardiac effects

a. ↓ automaticity, conduction velocity and excitability of cardiac cells.

b. Preferentially blocks open Na channels

c. Recovery from block slow in depolarized tissue; lengths refractory period (RP)

d. All effects are potentiated in depolarized tissues

e. Increases action potential duration (APD) and prolongs AP repolarization via block of K channels; decreases re-entry

f. Indirect action: anticholinergic effect (accelerates heart), which can speed A-V conduction.

---

**Actions & Toxicity of Quinidine**

Extracardiac

a. Blocks alpha-adrenoreceptors to yield vasodilatation.

b. Other strong antimuscarinic actions

Toxicity

- "Quinidine syncope"(fainting)- due to disorganized ventricular tachycardia
- associated with greatly lengthened Q-T interval; can lead to Torsades de Pointes (VT, precursor to ventricular fibrillation)
- negative inotropic action (decreases contractility)
- GI - diarrhea, nausea, vomiting
- CNS effects - headaches, dizziness, tinnitus (quinidine "Cinchonism")

Prolonged QT interval

Torsades de pointes "twisting of the points"
Quinidine: Pharmacokinetics/therapeutics

a. Oral, rapidly absorbed, 80% bound to membrane proteins
b. Hydroxylated in liver; T1/2 = 6-8 h
c. Drug interaction: displaces digoxin from plasma binding sites; so avoid giving drugs together or reduce dose
d. Probably are active metabolites of quinidine
e. Effective in treatment of nearly all dysrhythmias
f. Useful in treating chronic dysrhythmias requiring outpatient treatment

Procainamide (Class 1A) also Disopyrimide

Cardiac effects
a. Similar to quinidine, less muscarinic & alpha-adrenergic blockade
b. Has negative inotropic action also

Extracardiac effects
a. Ganglionic blocking reduces peripheral vascular resistance

Toxicity
a. Cardiac: Similar to quinidine, cardiac depression, QT interval
b. Noncardiac: Syndrome resembling lupus erythematosus

Pharmacokinetics/therapeutics
a. Administered orally, i.v b. Major metabolite in liver is N-acetylprocainamide (NAPA), a weak Na channel blocker with class III activity. Population of rapid acetylators who can accumulate high levels of NAPA.

c. T1/2 = 3-4 hours; necessitates frequent dosing; kidney chief elimination path. NAPA has longer T1/2 and can accumulate
d. Usually used short-term. Commonly used in CCUs for ventricular dysrhythmias associated with acute myocardial infarctions (MI)

Lupus erythematosus

- Chronic inflammatory disease
- Autoimmune disease

Drug induced: Procainamide, Hydralazine, Isoniazid

Lidocaine (Class IB prototype)

Other examples: Mexiletine, Phenytoin, Tocainide

General
a. Given i.v. (old ICU “drug of Choice” for VT)
b. Low toxicity (especially cardiac, good therapeutic index)
c. A local anesthetic, works on nerve at higher doses

Pharmacokinetics/therapy
a. i.v, since extensive first pass hepatic metabolism
b. T1/2 = 0.5-4 hours
c. Effective in suppressing dysrhythmia associated with depolarization (schemia; digitalis toxicity); ineffective against dysrhythmias in normal tissue.
d. Suppresses ventricular tachycardia; prevents fibrillation after acute MI; rarely used in supraventricular dysrhythmias.
e. Generally second line therapy that is refractory

Lidocaine Actions

Cardiac effects
a. Generally decreases APD, hastens AP repolarization, decreases automaticity and increases refractory period in depolarized cells.
b. Exclusively acts on Na channels in depolarized tissue by blocking open and inactivated (mainly) Na channels
c. Potent suppresser of abnormal activity
d. Most Na channels of normal cells rapidly unblock from lidocaine during diastole; few electrophysiological effects in normal tissue

Toxicity:
- least cardiotoxic, high dose can lead to hypotension
- tremors, nausea, slurred speech, convulsions

Phenytoin (Class IB)

1. Non-sedative anticonvulsant used in treating epilepsy (“Dilantin”)
2. Limited efficacy as antidyssrhythmic (second line antiarrhythmic)
3. Suppresses ectopic activation by blocking Na and Ca channels
4. Especially effective against digitalis-induced dysrhythmias
5. T1/2 = 24 hr – metabolized in liver
6. Gingival hyperplasia (40%)
7. Pregnancy Category D; Use not recommended
Gingival Hyperplasia

- Phenytoin (Dilantin) – anticonvulsant (40%)
- Calcium blockers – especially nifedipine (<10%)
- Cyclosporine – immunosuppressant (30%)

Flecainide (Class IC prototype)

Other examples: Lorcanide, Propafenone, Indecainide, Moricizine

1. Decreases automaticity, conduction in depolarized cells.
2. Marked block of open Na channels (decreases Ph 0); no change repolarization.
3. Used primarily for ventricular dysrhythmias but effective for atrial too
4. No anti muscularic action
5. Suppresses premature ventricular contractions (PVCs)
6. Associated with significant mortality; thus, use limited to last resort applications like treating ventricular tachycardias
7. Significant negative inotropic effect

Propranolol (Class II, beta-adrenoreceptor blockers)

Other agents: Metoprolol, Esmolol (short acting), Sotalol (also Class III), Acesulfamol

a. Slow A-V conduction
b. Prolong A-V refractory period
c. Suppress automaticity

Cardiac effects (of propranolol), a non-selective beta blocker

a. Main mechanism of action is block of beta receptors; ↓ Ph 4 slope. which decreases automaticity under certain conditions
b. Some direct local anesthetic effect by block of Na channels (membrane stabilization) at higher doses
c. Increases refractory period in depolarized tissues
d. Increases A-V nodal refractory period

Non-cardiac: Hypotension

Therapeutics

a. Blocks abnormal pacemakers in cells receiving excess catecholamines (e.g. pheochromocytoma) or up-regulated beta-receptors (e.g. hyperthyroidism)
b. Blocks A-V nodal reentrant tachycardias
c. Beta-blockers are used to treat supraventricular tachyarrhythmias (SVT)
d. Propranolol CI in decompenated ventricular failure; can lead to A-V block.

Oral (propranolol) or IV. Extensive metabolism in liver.

Beta-Adrenoceptor Antagonists

Properties of several beta-receptor blocking drugs

Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Ang</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β₁/β₂</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>for glaucoma</td>
</tr>
<tr>
<td>Acesulfamol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>also K-channel blocker</td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>long acting</td>
</tr>
<tr>
<td>Acetaminol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; short acting, operative arrhythmia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; long acting</td>
</tr>
</tbody>
</table>

Cardiac Action Potentials

Ion Flow

<table>
<thead>
<tr>
<th>nM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Na⁺/Ca²⁺ - exchange (3:1)

Na⁺/K⁺ - ATPase (3:2)
Clinical uses: Beta-Blockers

- **Hypertension:** frontline agents
- **Angina (non-selective or β1-selective):**
  - Cardiac: ↓O₂ demand more than O₂ supply
  - Exercise tolerance ↑ in angina patients
- **Arrhythmia (β1-selective, LA-action):**
  - ↓ SNS-induced increases in conductivity and automaticity
- **Glaucome (non-selective):**
  - ↓ aqueous humor formation (Timolol)
- **Congestive Heart Failure (non-selective or β1-selective):**
  - CI: unstable CHF, bronchospasm, depression, bradycardia
- **Other:**
  - Block of tremor of peripheral origin (β2-AR in skeletal muscle)
  - Migraine prophylaxis (mechanism unknown)
  - Hyperthyroidism: ↓ cardiac manifestation (only propranolol)
  - Panic attacks, stage fright

β-Blockers: Untoward Effects, Cautions

- Supersensitivity: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (ie. pindolol).
- Cardiac: ↓ reserve, fatigue, dizziness
- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance, β1-selective better
- Diabetes: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- Raynaud D: Decreased peripheral circulation
- CNS: nightmares, mental depression, insomnia
- Elderly: ↓ Effectiveness, ↑ adverse effects (ie. depression)

Cardiac effects of Amiodarone

a. Block Na channels (1A), but low affinity for open channels; mainly blocks inactivated Na channels
b. Block is most pronounced in tissues with long action potentials
c. Weak Ca channel blocker also (Class IV activity)
d. A powerful inhibitor of abnormal automaticity, decreases conduction, increases refractory period and APD.
e. Has antianginal effects (blocks alpha/beta receptors and Ca channels)

Extracardiac effects: Vasodilation via block of Ca channels and alpha receptors

Amiodarone: Only Antiarrhythmic with All Four Vaughan-Williams’ Class Effects

Class I effect
- Sodium channel blockade

Class II effect
- Noncompetitive alpha- and beta-adrenergic inhibition

Class III effect
- Prolongation of repolarization and refractoriness by increased APD

Class IV effect
- Calcium channel blockade

Amiodarone: Only DOC for Ventricular Dysrhythmias

- Sinus bradycardia, increase QT interval → ↑ risk TdP
- Negative inotropic action due to block of Ca channels and beta receptors, but can improve heart failure via vasodilation.
- A-V block, paradoxical VTs.

B. Non-cardiac:

- Deposits into almost every organ
- Reduces clearance of drugs like procainamide, flecainide, digitals, quinidine and diltiazem.
- Thyroid dysfunction (hypo or hyperthyroidism), contains iodine
- Pulmonary fibrosis is most serious adverse effect
- Paresthesias (tingling, prickling, or numbness)
- Photosensitivity
- Corneal microdeposits and blurred vision
- Ataxia, dizziness, tremor
- Anorexia, nausea

Amiodarone (Class III)

- Ibuutilide, Bretylium, Sotalol, Dofetilide
- Dronedarone (Jul 2009)

General

- New DOC for ventricular dysrhythmias (Lidocaine, old DOC)
- Prolongs refractory period by blocking potassium channels
- Also member of Classes IA,II,III,IV since blocks Na, K, Ca channels and alpha and beta adrenergic receptors
- Serious side effects (cardiac depression, pulmonary fibrosis, thyroid)
- Effective against atrial, A-V and ventricular dysrhythmias
- Widely used, very long acting (>25 d)

Adverse effects: Amiodarone

A. Cardiac

i. Sinus bradycardia, increase QT interval → ↑ risk TdP
ii. Negative inotropic action due to block of Ca channels and beta receptors, but can improve heart failure via vasodilation.
iii. A-V block, paradoxical VTs.

B. Non-cardiac:

i. Deposits into almost every organ
ii. Reduces clearance of drugs like procainamide, flecainide, digitals, quinidine and diltiazem.
iii. Thyroid dysfunction (hypo or hyperthyroidism), contains iodine
iv. Pulmonary fibrosis is most serious adverse effect
v. Paresthesias (tingling, prickling, or numbness)
vi. Photosensitivity
vii. Corneal microdeposits and blurred vision
viii. Ataxia, dizziness, tremor
ix. Anorexia, nausea
Pulmonary fibrosis

Dronedarone ~ 24 hr
- \( T_{1/2} = 13-103 \text{ days} \) (weeks) very long for one dose; very lipid soluble; metabolized in liver
- Effective against many arrhythmias: atrial, A-V and ventricular dysrhythmias; prevention of atrial fibrillation/flutter; PVCs, nonsustained & sustained VTs.
- Multiple interactions with other drugs such as:
  i. Amiodarone is a CYP3A4 substrate and inhibitor and thus may enhance the effect of other CYP3A4 substrates eg. Warfarin, Simvastatin, Verapamil
  ii. Amiodarone may increase the serum concentration of Cardiac Glycosides

Ibutilide (Class III).
1. Prolongs cardiac action potential
2. Administered I-V. Most effective current agent to convert atrial fibrillation and flutter of recent onset to normal rhythm. Low incidence of Torsades de Pointes (Tdp, about 2%), compared to other drugs.
3. More effective for atrial flutter than fibrillation
4. Generally well tolerated

Sotalol (Class III and Class II)
1. Non-selective beta blocker,
2. Increases AP duration, increase QT interval
3. Uses: dysrhythmias of supraventricular (very effective) & ventricular origin

Amiodarone: Pharmacokinetics and therapeutics
Dronedarone ~ 24 hr
- \( T_{1/2} = 13-103 \text{ days} \) (weeks) very long for one dose; very lipid soluble; metabolized in liver
- Effective against many arrhythmias: atrial, A-V and ventricular dysrhythmias; prevention of atrial fibrillation/flutter; PVCs, nonsustained & sustained VTs.
- Multiple interactions with other drugs such as:
  i. Amiodarone is a CYP3A4 substrate and inhibitor and thus may enhance the effect of other CYP3A4 substrates eg. Warfarin, Simvastatin, Verapamil
  ii. Amiodarone may increase the serum concentration of Cardiac Glycosides

Verapamil (Class IV, Ca++ channel blockers)
Other example: Diltiazem - CCBs increasing use and importance
- Blocks active and inactivated Ca channels, prevents Ca entry
- More effective on depolarized tissue. Issue firing frequently or areas where activity dependent on Ca channels (SA node; A-V node)
- Increases A-V conduction time and refractory period; directly slows SA and A-V node automatically
- Suppresses oscillatory depolarizing after depolarizations due to digoxis
- Dihydropyridine CCBs are generally poor antiarrhythmics

Bretlyium (Class III, K+ channel blockers)
Others Amiodarone, Ibutilide, (Sotalol, also beta-blocker)
General: originally used as an antihypertensive agent
Cardiac effects
- a. Direct antidyssrhythmic action
- b. Increases ventricular APD and increases refractory period; decreases automatically
- c. Most pronounced action in ischemic cells having short APD
- d. Initially stimulates and then blocks neuronal catecholamine release from adrenergic nerve terminals
- e. Blocks cardiac K channels to increase APD

Extracardiac effects: Hypotension (from block of NE release)

Pharmacokinetics/therapeutics
- a. In or intramuscular
- b. Excreted mainly by the kidney
- c. Usually for emergency use only. Increases threshold for fibrillation.
- d. Decreases tachycardias and early extrasystoles by increasing effective refractory period

Ca++ Channel Blockers - Actions
Extracardiac
- a. Peripheral vasodilatation via effect on smooth muscle
- b. Used as antianginal / antihypertensive
- c. Hypotension may increase HR reflexively

Toxicity
- a. Cardiac
  - Negative inotropic for damaged heart, depresses contractility
  - Can produce complete A-V block
- b. Extracardiac
  - Hypotension
  - Constipation, nervousness
  - Gingival hyperplasia

Pharmacokinetics/Therapeutics
- a. \( T_{1/2} = 7 \text{h} \), metabolized by liver
- b. Oral administration; also available parenterally
- c. Caution for patients with liver disease
- d. Decrease reentrant supraventricular tachycardia (A-V nodal conduction), decreases atrial flutter and fibrillation
- e. Only moderately effective against ventricular arrhythmias
Dysrhythmics - Others

A. Adenosine: i.v. (15 secs), activates P1 purinergic receptors (A1) coupled to K channels, ↓CV, ↑refractory period. SVT. Flushing, hypotension, burning sensation

B. Potassium ions (K+): Depress ectopic pacemakers - can depress CV → reentrant dysrhythmia

C. Digoxin: used to treat atrial flutter and fibrillation - AV node ↓conduction (vagal stimulation) - myocardium ↓refractory period - Purkinje fibers ↑refractory period, ↓conduction

D. Magnesium: used to treat Torsades de Pointes

E. Autonomic agents: used to treat A-V block - β-agonists (ie.EPI), anticholinergics (ie. atropine)

Anticoagulant therapy:
- prevent formation of systemic emboli & stroke

Drug interactions involving antidysrhythmics

A. These drugs must be used very carefully
B. Sometimes interactions can be counter-intuitive

Problems with selecting drugs:
A. Do not always know the cause of the dysrhythmia, thus what to treat?
B. Multiple mechanisms of dysrhythmogenesis
C. Drugs are both anti- and pro-dysrhythmias
D. Drugs do not really fix the damage; usually they restore function by breaking something else

Cardiac Effects of Antiarrhythmic Drugs

<table>
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<tr>
<th>Drug</th>
<th>Class</th>
<th>Auto</th>
<th>CV</th>
<th>SP</th>
<th>APD</th>
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More important agents