Agents used in HT, CHF, Arrhythmia 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</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF (CI: unstable HF, bronchospasm, significant bradycardia, depression); Raynaud D. Caution in diabetes, asthma (use β1-)</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF, constipation, gingival hyperplasia, edema, reflex tachycardia</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angioedema, hyperkalemia, cough (acei), tetrogenic, glossitis, taste</td>
</tr>
<tr>
<td>Diuretics (Thiazides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR &gt;30, hypokalemia (CG); ↑Ca++, diabetes (↓glucose tolerance)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Many Rx interactions, [K+], ↓use HF important, low K+→↑toxicity,</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flushing, dizziness, headache, nausea, reflex tachycardia</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effects enhanced in depolarized, damaged tissue, Phase 0, ↓CV</td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NO/cGMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>
Can't see the forest for the trees

Hung up on the detail, you can not see the big picture

Heart Physiology

Closed system
Supply nutrients/O₂

Pressure driven
Remove metabolites
Heart Physiology

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>atria depolarization</td>
</tr>
<tr>
<td>QRS</td>
<td>ventricle depolarization</td>
</tr>
<tr>
<td>PR</td>
<td>conduction A-V</td>
</tr>
<tr>
<td>T</td>
<td>ventricle repolarization</td>
</tr>
<tr>
<td>QT</td>
<td>duration ventricle of repolarization</td>
</tr>
</tbody>
</table>

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

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
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
Classification of dysrhythmias

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)

Examples of Arrhythmias

The EKG breaks down each heartbeat into a series of electrical waves. Three of the waves, the P wave, the QRS complex and the T wave, are associated with the heart's contractions. The P wave reflects activity in the heart's upper chambers. The QRS complex and T wave reflect activity in the lower chambers.
Ion Permeability

<table>
<thead>
<tr>
<th>mM</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>

0 Na⁺⁺ - open
1 Na⁺ - close
   K⁺ - open/close
2 Ca⁺⁺ - open
   K⁺ - leak
3 Ca⁺⁺ - close
   K⁺ - open
4 K⁺ - close

Na⁺/Ca⁺⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)

Cardiac Action Potentials
Ion Flow

<table>
<thead>
<tr>
<th>mM</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>

0 Na⁺⁺ - open
1 Na⁺ - close
   K⁺ - open/close
2 Ca⁺⁺ - open
   K⁺ - leak
3 Ca⁺⁺ - close
   K⁺ - open
4 K⁺ - close

Na⁺/Ca⁺⁺ - 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

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

Abnormal impulse conduction: Reentry
Unidirectional Block

Damaged tissue is usually depolarized → ↓ conduction velocity

A. Normal

Nerve impulse

Ventricle wall

B. Unidirectional Block

Impulse blocked in one direction

Impulse travels in retrograde direction and reenters the conduction pathway causing an extra or irregular heart beat.

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
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>IA.</td>
<td>Moderate Na block Ph.0; slow conduction; ↑ APD</td>
<td>Quinidine, Procainamide</td>
</tr>
<tr>
<td>IB.</td>
<td>Minimal Na block Ph.0; slow conduction (less); shorten Ph.3 repolarization</td>
<td>Lidocaine, Phenytoin</td>
</tr>
<tr>
<td>IC.</td>
<td>Marked Na block Ph.0; slow conduction; no change APD or repolarization. Increased suppression of Na channels</td>
<td>Flecainide, 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, others</td>
</tr>
<tr>
<td>Class III</td>
<td>Prolong repolarization/refractory period other means than exclusively iNa block (mainly K+ channel blockade).</td>
<td>Amiodarone, 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, Diltiazem</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.

3. **Single class can effect multiple mechanisms.** Amiodarone: properties of classes (I-IV).

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.

---

**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 action potential duration

- **Class IV effect**
  Calcium channel blockade
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.

Drugs work better on depolarized tissue.....
Key Aspects of Drug Action and Therapy...

a. Drug action is state-dependent: channel open, closed, or inactivated. Two current models:
   i. modulated receptor hypothesis: different states have different affinities
   ii. guarded receptor hypothesis: channel gate limits drug access to site

b. Drugs selectively affect firing and conduction in abnormal/depolarized cells.

c. Transitions between states dependent on membrane voltage and cell firing frequency, membrane voltage and spike frequency. Binding to inactivated states and slowing recovery from inactivation, some drugs can increase the time needed for recovery from inactivation.
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; lengthens 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 reentry

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; $T_{1/2} = 6-8$ 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, including:
   1) Premature atrial contractions
   2) Paroxysmal atrial fibrillation and flutter
   3) Intra-atrial and A-V nodal reentrant dysrhythmias
   4) Wolff-Parkinson-White tachycardias (SVT, A-V bypass)
   5) Premature ventricular contractions (PVCs)

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

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. Bimodal distribution in population of rapid acetylators, who can accumulate high levels of NAPA.

c. $T_{1/2} = 3-4$ hours; necessitates frequent dosing; kidney chief elimination path. NAPA has longer $T_{1/2}$ and can accumulate

d. Usually used short-term. Commonly used in CCUs for ventricular dysrhythmias associated with acute myocardial infarctions (MI)
**Lidocaine (Class IB prototype)**

**Other examples:** Mexiletine, Phenytoin, Tocainide

**General**
- Commonly used antidysrhythmic agent in emergency care (decreasing use)
- Given i-v; widely used in ICU-critical care units (old DOC, prior 2001)
- Low toxicity (especially cardiac, good therapeutic index)
- A local anesthetic, works on nerve at higher doses

**Lidocaine Actions**

**Cardiac effects**
- Generally decreases APD, hastens AP repolarization, decreases automaticity and increases refractory period in depolarized cells.
- Exclusively acts on Na channels in depolarized tissue by blocking open and inactivated (mainly) Na channels
- Potent suppresser of abnormal activity
- 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

**Pharmacokinetics/therapy**
- i-v, since extensive first pass hepatic metabolism
- $T_{1/2} = 0.5-4$ hours
- Effective in suppressing dysrhythmia associated with depol. tissue (ischemia; digitalis toxicity); ineffective against dysrhythmias in normal tissue (atrial flutter).
- Suppresses ventricular tachycardia; prevents fibrillation after acute MI; rarely used in supraventricular dysrhythmias
Phenytoin (Class IB)

1. Non-sedative anticonvulsant used in treating epilepsy ('Dilantin')
2. Limited efficacy as antidysrhythmic (second line antiarrythmic)
3. Suppresses ectopic activation by blocking Na and Ca channels
4. Especially effective against digitalis-induced dysrhythmias
5. $T_{1/2} = 24$ hr – metabolized in liver
6. Gingival hyperplasia (40%)

Gingival Hyperplasia

- Phenytoin (Dilantin) – anticonvulsant (40%)
- Calcium blockers – especially nifedipine (<10%)
- Cyclosporine – immunosuppressant (30%)
**Flecainide (Class IC prototype)**

Other examples: Lorcanide, Propafenone, Indecainide, Moricizine
Depress rate of rise of AP without change in refractoriness or APD
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 antimuscarinic 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), Acebutolol
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 (ie. hyperthyroidism)
b. Blocks A-V nodal reentrant tachycardias; inhibits ectopic foci
c. Beta-blockers are used to treat supraventricular tachydyssrhythmias
d. Propranolol contraindicated in ventricular failure; can lead to A-V block.

Oral (propranolol) or IV. Extensive metabolism in liver.
Cardiac Action Potentials
Ion Flow

<table>
<thead>
<tr>
<th>mM</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>

- 0 Na⁺ - open
- 1 Na⁺ - close
  K⁺ o - open/close
- 2 Ca²⁺ - open
  K⁺ o - leak
- 3 Ca²⁺ - close
  K⁺ o - open
- 4 K⁺ - close

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

Beta-Adrenoceptor Antagonists

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anaesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β₁</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-9 hours</td>
<td>40</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14-22 hours</td>
<td>90</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9-12 hours</td>
<td>80</td>
</tr>
<tr>
<td>Cardisol</td>
<td>None</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
</tr>
<tr>
<td>Cephranol</td>
<td>β₂</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>4-5 hours</td>
<td>70</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₂</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>...</td>
</tr>
<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes¹</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₂</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14-24 hours</td>
<td>33</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Prazosin</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3-4-6 hours</td>
<td>30¹</td>
</tr>
<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>90</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-6 hours</td>
<td>50</td>
</tr>
</tbody>
</table>

¹Partial agonist effects at β₁ receptors. ²Labetalol also causes α₁-selective blockade. ³Bioavailability is dose-dependent.
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

- **Glaucoma (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

### Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β₁/β₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>α-blocking activity</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>long acting</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>MSA; prototypical beta-blocker</td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></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></td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td>β₁-selective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>MSA</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
β-Blockers: Untoward Effects, Cautions

• Supersensitivity: Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal

• Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective agents preferred

• 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

• Elderly: Effectiveness is decreased, more CNS effects (ie. depression)

Amiodarone (Class III)
others: Ibutilide, Bretylium, Sotalol, Dofetilide
Dronedarone (Jul 2009)

General

a. New DOC for ventricular dysrhythmias (Lidocaine, old DOC)
b. prolongs refractory period by blocking potassium channels
c. also member of Classes IA,II,III,IV since blocks Na, K, Ca channels and alpha and beta adrenergic receptors
d. serious side effects (cardiac depression, pulmonary fibrosis, thyroid)
e. effective against atrial, A-V and ventricular dysrhythmias
f. widely used, very long acting (>25 d)
AHA Guidelines for VT/VF 2001

1. Amiodarone
2. Procainamide, [Bretylium]
3. Sotalol
4. Lidocaine

AHA Guideline Prior to 2001

1. Lidocaine
2. Procainamide
3. Bretylium
4. Electrical cardioversion

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
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, digitalis, quinidine and diltiazem.
   iii. **Thyroid dysfunction** *(hypo or hyperthyroidism)*
   iv. **Pulmonary fibrosis** is most serious adverse effect
   v. Paresthesias (tingling, pricking, or numbness)
   vi. Photosensitivity
   vii. **Corneal microdeposits** and blurred vision
   viii. Ataxia, dizziness, tremor
   ix. Anorexia, nausea

---

**Pulmonary fibrosis**

**Inflammatory Cells**
- Macrophages
- Lymphocytes

**Parenychmal Cells**
- Endothelial Cells
- Epithelial Cells

**Gas Exchange**
- Normal Alveoli
- Epithelial Disruption

**Fibroblast Activation**
- Extracellular Matrix Remodeling

**Pulmonary Fibrosis**

Prolonged QT interval
Amiodarone: Pharmacokinetics and therapeutics
Dronedarone ~ 24 hr

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

Bretylium (Class III, K+ channel blockers)

- **Others** Amiodarone , Ibutilide, (Sotalol, also beta-blocker)

General: originally used as an antihypertensive agent

Cardiac effects
- a. Direct antidysrhythmic action
- b. Increases ventricular APD and increases refractory period; decreases automaticity
- 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. iv or intramuscular
- b. Excreted mainly by the kidney
- c. Usually for emergency use only: ventricular fibrillation when lidocaine and cardioversion therapy fail. Increases threshold for fibrillation.
- d. Decreases tachycardias and early extrasystoles by increasing effective refractory period
Ibutilide (Class III).

1. Prolongs cardiac action potential without additional effects.
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 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

Verapamil (Class IV, Ca++ channel blockers)

Other example: Diltiazem - CCBs increasing use and importance

a. Blocks active and inactivated Ca channels, prevents Ca entry
b. More effective on depolarized tissue, tissue firing frequently or areas where activity dependent on Ca channels (SA node; A-V node)
c. Increases A-V conduction time and refractory period; directly slows SA and A-V node automaticity
d. suppresses oscillatory depolarizing after depolarizations due to digitalis
e. Dihydropyridine CCBs are generally poor antiarrhythmics
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
   - Too 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. Blocks reentrant supraventricular tachycardia ("A-V nodal reentrant tachycardia"), 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>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Auto</th>
<th>CV</th>
<th>RP</th>
<th>APD</th>
<th>ANS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IB</td>
<td>↓</td>
<td>0</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td>↓</td>
<td>0</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td>↓</td>
<td>0</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>II</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>β-block</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>β-block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>II</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>β-block</td>
</tr>
<tr>
<td>Sotalol</td>
<td>II/III</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>β-block</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>α-, β-block</td>
</tr>
<tr>
<td>Bretylium</td>
<td>III</td>
<td>↓</td>
<td>0</td>
<td>↑</td>
<td>↑</td>
<td>Sympatholytic</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IV</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>Other</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>vagal stimulation</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Other</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

More important agents
### Pharmacokinetic Properties of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Plasma Binding %</th>
<th>T½ (hrs)</th>
<th>Drug Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>60</td>
<td>6</td>
<td>20-40%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td>15</td>
<td>4</td>
<td>60%</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>39-95</td>
<td>5</td>
<td>50-70%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IB</td>
<td>40</td>
<td>2</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td>10</td>
<td>14</td>
<td>40%</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td>65</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>45</td>
<td>15</td>
<td>40%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>II</td>
<td>90</td>
<td>4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>15</td>
<td>4</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>II</td>
<td>(hydro. esterase)</td>
<td>9 min</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>9</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>95</td>
<td>&gt; 25 days</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bretylium</td>
<td>III</td>
<td>5</td>
<td>9</td>
<td>80%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IV</td>
<td>90</td>
<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Misc</td>
<td></td>
<td>15 sec</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Dysrhythmia Treatment

**Treatment**
- Acute vs Chronic

**Site**
- Ventricular vs Supraventricular
Considerations for treating Dysrrhythmias

1. Acute vs chronic treatment
2. Ventricular vs supraventricular

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular</td>
<td>Adenosine, Digoxin</td>
<td>Beta-blocker, Calcium antagonist</td>
</tr>
<tr>
<td>Ventricular</td>
<td>Amiodarone, Procainamide, Sotalol, Bretylium, Lidocaine</td>
<td>Amiodarone, Sotalol, Flecainide</td>
</tr>
</tbody>
</table>

Antiarrhythmics Question 1

When used as an antiarrhythmic agent, procainamide typically?

a. increases cardiac contractility
b. increases action potential duration
c. increases AV conduction
d. decreases QT interval
e. decreases Na-channel recovery time