HST-151   1
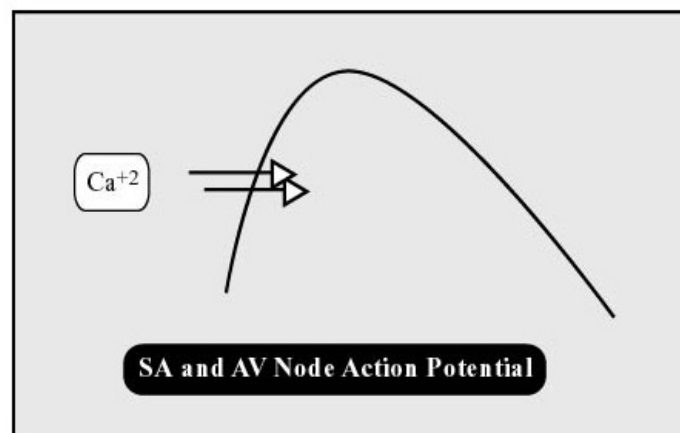
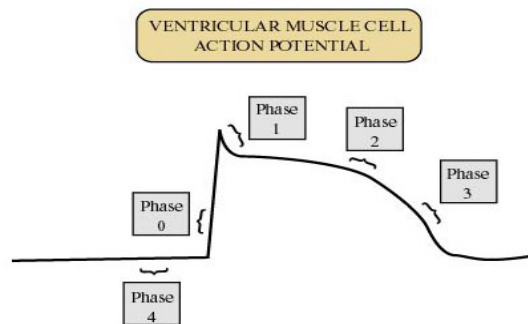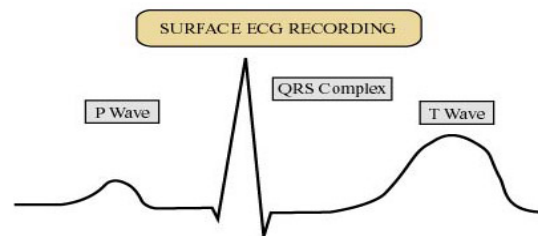# Antidysrhythmics

I. **Ventricular muscle cell action potential**
    a. Phase 0: Upstroke
    b. Phase 1: Early-fast repolarization
    c. Phase 2: Plateau
    d. Phase 3: Repolarization
    e. Phase 4: Diastole

II.   Cardiac arrhythmia:
   a. Abnormal impulse formation
       i. Early afterdepolarizations (EADs): interrupts phase 3 -
           exacerbated at slow heart rates and may contribute to development
           of long QT-related arrhythmias

Early Afterdepolarizations
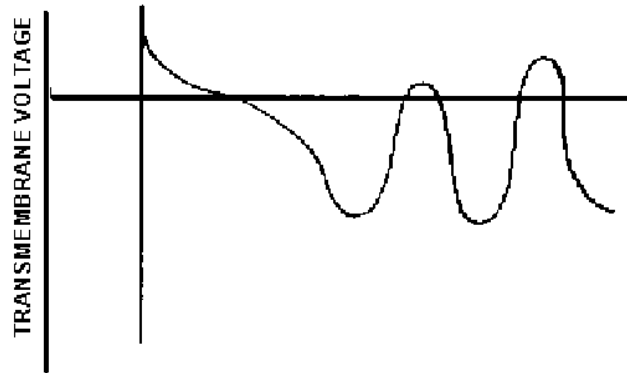
       ii. Delayed afterdepolarizations (DADs): interrupts phase 4 - occurs
            when intracellular calcium is increased; is exacerbated by fast
            heart rates, may relate to digitalis excess, catecholamines, and
            myocardial ischemia
   b. Abnormal impulse propagation:
       i. Abnormal depolarization (QRS)
       ii. Abnormal repolarization (QT_c)

III.   Cellular mechanism of arrhythmia:
   a. Enhanced automaticity: sinus and AV node, His-Purkinje system
       i. Beta-adrenergic stimulation, hypokalemia, mechanical stretch
           increase phase 4 slope & pacemaker rate
   b. Reentry: impulse reenters and excites areas of the heart more than once
       i. Obstacle for homogeneous conduction (anatomic, physiologic)
       ii. Unidirectional block in conduction circuit
       iii. Path length X conduction velocity > refractory period

  c. Polymorphic ventricular tachycardia (Torsades de Pointes): ("twisting of the points") or drug-induced long QT syndrome (DILQTS)

- Polymorphic arrhythmia that can rapidly develop into ventricular fibrillation

- Associated with drugs that have Class III actions (potassium channel blockers)

  - Also seen with other drugs such as terfenadine, cisapride, under certain circumstances

- Usually occurs within the first week of therapy

- Preexisting prolonged QTc intervals may be indicator of susceptibility

- Potentiated by bradycardia

- Often associated with concurrent electrolyte disturbances (hypokalemia, hypomagnesemia)

IV. Classification of Antiarrhythmic drugs:

- Although several of the drugs used to treat cardiac arrhythmias have been used for many years (e.g.- quinidine and digitalis since the early 1900s), most of the agents approved for use today have only been available for a decade or less.

- Research in recent years has provided much information regarding the cellular mechanisms of arrhythmias and the mechanisms by which some of the antiarrhythmic drugs act, but the general approach to antiarrhythmic therapy remains largely empirical.

- The recent results of several clinical trials, including the Cardiac Arrhythmia Suppression Trial (CAST), have indicated that many antiarrhythmic drugs may significantly increase mortality compared to placebo.

  - All of the antiarrhythmic drugs act by altering ion fluxes within excitable tissues in the myocardium. The three ions of primary importance are Na^+, Ca^{++}, and K^+. Antiarrhythmic drugs can be classified by their ability to directly or indirectly block flux of one or

more of these ions across the membranes of excitable cardiac muscle
cells.

- Class I drugs, those that act by blocking the sodium channel, are subdivided into 3
  subgroups, IA, IB, and IC based on their effects on repolarization and potency
  towards blocking the sodium channel

  - Subclass IA drugs have high potency as sodium channel blockers (prolong
    QRS interval), and also usually prolong repolarization (prolong QT
    interval) through blockade of potassium channels

  - Subclass IB drugs have the lowest potency as sodium channel blockers,
    produce little if any change in action potential duration (no effect on QRS
    interval) in normal tissue, and shorten repolarization (decrease QT
    interval)

  - Subclass IC drugs are the most potent sodium channel blocking agents
    (prolong QRS interval), and have little effect on repolarization (no effect
    on QT interval)

- Class II drugs act indirectly on electrophysiological parameters by blocking beta-
  adrenergic receptors (slow sinus rhythm, prolong PR interval, little effect on QRS
  or QT intervals)

- Class III drugs prolong repolarization (increase refractoriness) by blocking
  outward potassium conductance (prolong QT interval), with typically little effect
  on the rate of depolarization (no effect on QRS interval)

- Class IV drugs are relatively selective AV nodal L-type calcium-channel blockers
  (slow sinus rhythm, prolong PR interval, no effect on QRS interval)

- Miscellaneous In addition to the standard classes, IA-C, II, III, and IV, there is
  also a miscellaneous group of drugs that includes digoxin, adenosine, magnesium,
  alinidine (a chloride channel blocker) and other compounds whose actions don't
  fit the standard four classes
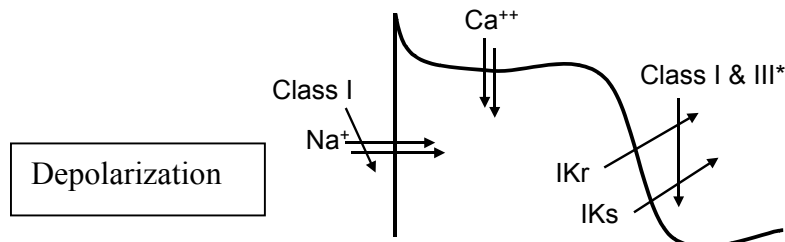
Ventricular Action Potential

Ca^{++}

Class I & III*

Class I

Na$^+$

Depolarization

IKr

IKs

Table 1. Vaughan Williams Classification of Antiarrhythmic Drugs

Class	Action	Drugs
I	Sodium Channel Blockade	
IA	Prolong repolarization	Quinidine, procainamide, disopyramide
IB	Shorten repolarization	Lidocaine, mexiletine, tocainide, phenytoin
IC	Little effect on repolarization	Encainide, flecainide, propafenone, moricizine(?)
II	Beta-Adrenergic Blockade	Propanolol, esmolol, acebutolol, *l*-sotalol
III	Prolong Repolarization (Potassium Channel Blockade; Other)	Ibutilide, dofetilide, sotalol (*d,l*), amiodarone, bretylium
IV	Calcium Channel Blockade	Verapamil, diltiazem, bepridil
Miscellaneous	Miscellaneous Actions	Adenosine, digitalis, magnesium

Table 2. Class Toxicities of Antiarrhythmic Drugs (Adapted from Woosley, 1991)

Class I	Class II	Class III	Class IV
Proarrhythmic effects: • IA- Torsades de pointes • IC- CAST proarrhythmia Negative inotropic effect Infranodal conduction block	Sinus bradycardia AV block Depression of LV function (adrenergic-dependent)	Sinus bradycardia Torsades de pointes	Sinus bradycardia AV block Negative inotropic effect

V.   Mechanism of antiarrhythmic drugs:

Antiarrhythmic drugs act by altering the flux of ions across the membranes of excitable cells in the heart. The primary mechanisms of action correspond to the mechanisms used in developing the Vaughan Williams classification system, and include inhibition of sodium channels (Class I drugs), inhibition of calcium channels (Class IV drugs), inhibition of potassium channels (Class III drugs), and blockade of beta-adrenergic receptors in the heart (Class II drugs).

a. Sodium Channel Blockade

- Sodium channels are responsible for the initial rapid (Phase 0) depolarization of atrial, Purkinje, and ventricular cells.

- Sodium channel activation (opening) is voltage-dependent

- The sodium current entering the cell during phase 0 depolarization is very intense, but brief

- Activation (opening) and inactivation (closing) of cardiac sodium channels is very rapid

- Blockade of sodium channels:

  o Slows the rate and amplitude of phase 0 depolarization

  o Reduces cell excitability

  o Reduces conduction velocity

- SA and AV nodal cells have relatively few sodium channels and therefore lack a rapid phase 0 depolarization.

b. Calcium Channel (L-type) Blockade

- Calcium channels (L-type) are responsible for the prolonged plateau phase (Phase 2) seen in the action potential of atrial, Purkinje, and ventricular cells.

- L-type calcium channel opening is voltage-dependent, but requires a more positive membrane potential than cardiac sodium channels

- The calcium current entering the cell during phase 2 is intense and prolonged

- L-type calcium channels are slow to activate (open) and slow to inactivate (close)

- Blockade of calcium channels reduces the amplitude and length (time) of phase 2 in atrial, Purkinje, and ventricular cells

- In SA and AV nodal cells, calcium entry through L-type channels represents the major ion flux during depolarization.

c. Potassium Channel Blockade

- Potassium channels, particularly the channel giving rise to the "delayed rectifier current", are activated during the repolarization (Phase 3) of the action potential.

- Blockade of potassium channels prolongs action potential duration.

  o Prolongation of action potential duration usually results in an increase in effective refractory period

d. Use (Rate)-Dependent Blockade by Channel Blockers

- An ideal antiarrhythmic drug should target ectopic pacemakers and rapidly depolarizing tissue to a greater extent than normal tissues of the heart

- Many of the sodium (Class I) and calcium (Class IV) channel blockers have this property because they preferentially block sodium and calcium channels in depolarized tissues (cf, Modulated Receptor Hypothesis in preceding lecture).

- Enhanced sodium or calcium channel blockade in rapidly depolarizing tissue has been termed "use-dependent blockade" and is thought to be responsible for increased efficacy in slowing and converting tachycardias with minimal effects on tissues depolarizing at normal (sinus) rates

- Many of the drugs that prolong repolarization (Class III drugs, potassium channel blockers) exhibit negative or reverse rate-dependence

  o These drugs have little effect on prolonging repolarization in rapidly depolarizing tissue

  o These drugs can cause prolongation of repolarization in slowly depolarizing tissue or following a long compensatory pause, leading to repolarization disturbances and torsades de pointes

IA

III

IC

II & IV
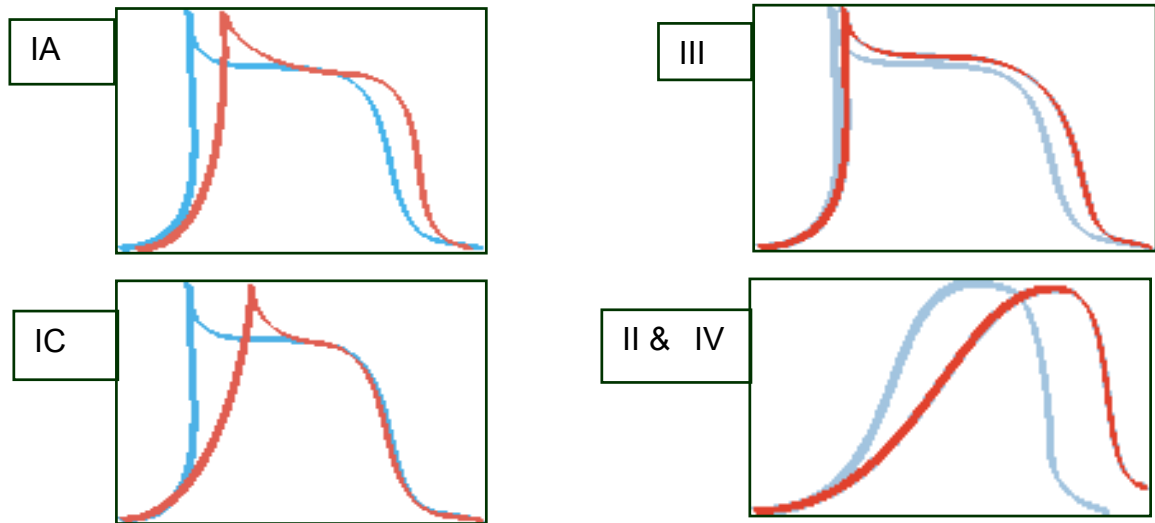
VI. **Acute Treatement of VT:**

    a. Lidocaine (50-75 mg bolus, 1-3 mg/min)

    b. Procainamide (500 mg – 1 g over 40-60 min, 1-4mg/min)

    c. Amidodarone (100 mg over 10 min, 1mg/min)

    d. Bretylium (300 mg over 1 hr, 1 mg/min)

    e. Magnesium sulfate

    f. DC cardioversion/defibrillation

VII. **Classification of SVT:**

   a. Sinus tachycardia:

        i. Physiologic

        ii. Nonphysiologic:

            1. Inappropriate sinus tachycardia (IST)

            2. Sinus node reentry (SNR)

    b. AV Node independent (Atrial)

        i. PACs

        ii. Atrial tachycardia

        iii. Atrial flutter

        iv. Atrial fibrillation

    c. AV node dependent (junctional)

        i. AV node reentry

        ii. AV reentry

    d. Junctional ectopic tachycardia (JET)

VIII.   SVT : ECG correlation:
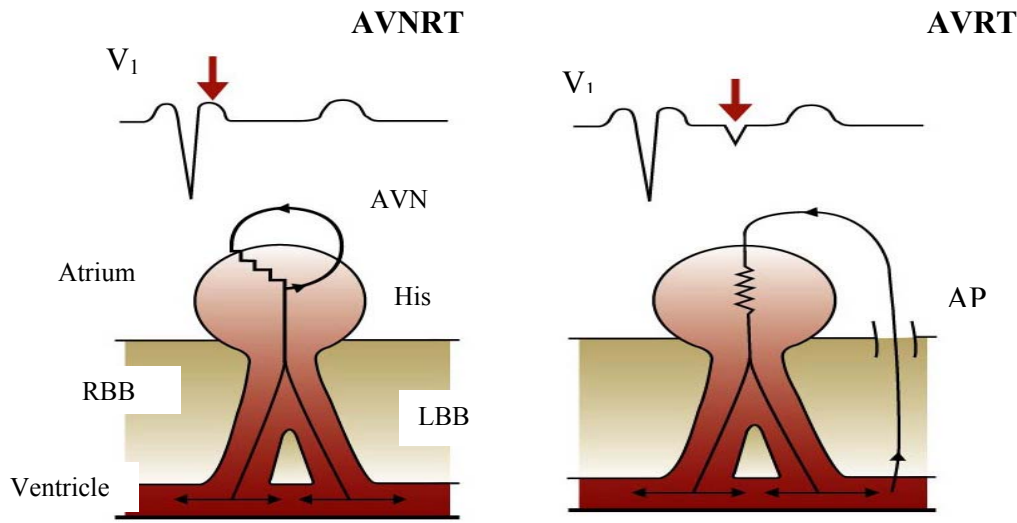
IX.   Antiarrhythmic drug effects in SVT:
  a.   AVN independent:
         i.   Prevent/terminate tachycardia
         ii. Slow ventricular rate
  b.   AVN depededent:
   i.   Prevent/terminate tachycardia
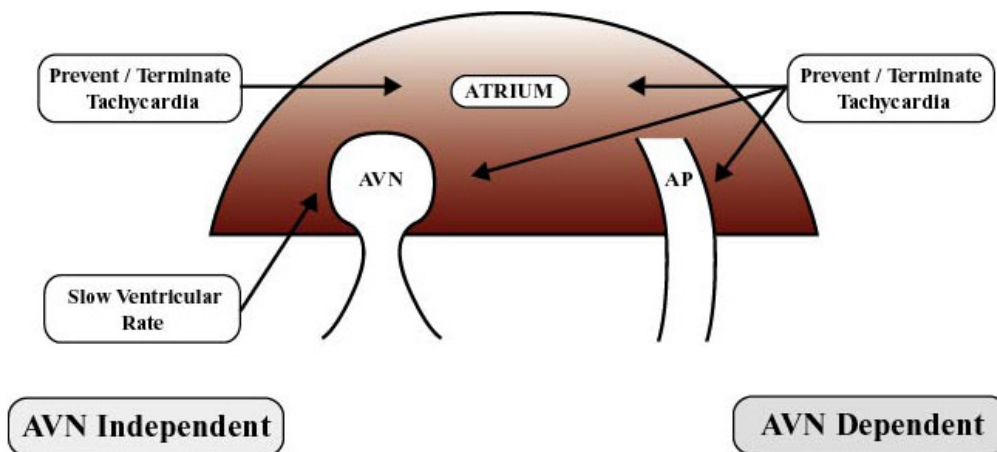
X.   Radiofrequency (RF) catheter ablation of left free wall accessory AV connection

  a.   Radiofrequency (RF) catheter ablation has recently replaced surgical ablation in nearly all cases of ablation for cardiac arrhythmias. It is now a first-line therapy and highly effective in treating:

        i. Wolff-Parkinson-White syndrome

       ii. AV nodal reentry

     iii. Atrial ectopic tachycardia

b. RF ablation is also useful in treating:

        i. Atrial fibrillation

       ii. Several types of monomorphic ventricular tachycardias

XI.   Clinical studies:

a. Cardiac Arrhythmia Suppression Trial (CAST): encainide or flecainide vs placebo
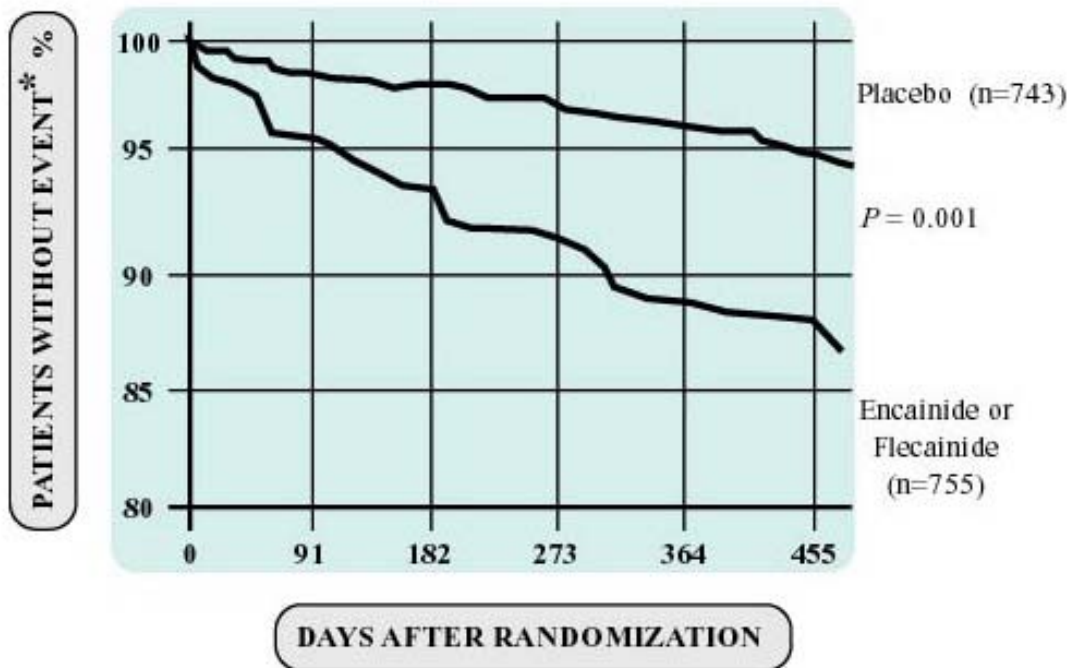
XII.   Antiarrhythmic in structural HD (VT)
  a. Beta blocker
  b. Sotalol
  c. Amiodarone

XIII.   Non-pharmacological Therapy
  a. Surgery
  b. Catheter ablation
  c. Implantable cardioverter-defibrillator (ICD)

XIV.   Automatic implatable cardioverter/defibrillator devices (ICDs) therapy circa 1980:
Large devices, abdominal site
  a. Thoracotomy, multiple incisions
  b. Long hospital stay
  c. General anesthesia
  d. Complication from major surgery
  e. Perioperative mortality up to 5%
  f. Nonprogrammable therapy
  g. High energy shock only
  h. Device longevity ~ 1.5 years
  i. Fewer than 1000 implants/year

XV.   ICD therapy present:
  a.   Can now be implanted without thoracotomy

  b. Current generation devices terminate arrhythmias by anticardiac pacing, cardioversion, and defibrillation

  c. Considered by some experts to be the therapy of first choice in patients with ventricular tachycardias based on a number of recent clinical trials comparing ICD therapy to antiarrhythmic drug therapy (both Class I and Class III drugs)

  d. A significant fraction of patients receiving an ICD may still require antiarrhythmic drug therapy to decrease the frequency of arrhythmic episodes (to prolong battery life) and to reduce the number of inappropriate (energy-consuming and painful) shocks. Improvements in ICD design may reduce or eliminate the need for concurrent drug therapy.

XVI.   Conclusions:
  a. Antiarrhythmic drugs are first line therapy for the **<u>acute</u>** management of most supraventricular and ventricular arrhythmias
  b. Catheter ablation is curative for most forms of recurrent SVTs

c. Life threatening ventricular arrhythmias are best managed with ICDs and adjunctive drug therapy when necessary

APPENDIX:

Therapeutics

- It is often problematic to determine the best drug for a given patient due to the unknown etiology of many arrhythmias, patient-to-patient variability, and the multiple actions of many antiarrhythmic drugs. Three trial-and-error approaches are widely used:

    o **Empiric.** That is, based upon the clinician's past experience.

    o **Serial drug testing guided by electrophysiological study (EPS).** This invasive technique requires cardiac catheterization and induction of arrhythmias by programmed electrical stimulation of the heart, followed by a delivery of drugs to predict the most efficacious drug(s) to use for a given patient.

    o **Drug testing guided by electrocardiographic monitoring (Holter monitoring).** This noninvasive technique involves 24-hour recording of a patient's ECG before and during each drug treatment to predict optimal efficacy. The recent Electrophysiologic versus Electrocardiographic Monitoring (ESVEM) study concluded that there may not be any significant difference between the predictive value of this technique compared to programmed electrical stimulation.

- Before beginning therapy:

    o Any factor that might predispose a patient to arrhythmias (electrolyte abnormalities, hypoxia, proarrhythmic drugs, underlying disease states) should be eliminated

    o A firm diagnosis should be made before beginning therapy and a baseline ECG should be established to monitor the efficacy of treatment

- Monitoring during therapy should include:

    o Continuous and careful monitoring for efficacy and adverse effects

    o Monitoring plasma concentrations of drug, including free vs. protein-bound because of the narrow therapeutic index of most antiarrhythmic drugs

Table 3. Drugs of Choice for Cardiac Arrhythmias (Adapted from The Medical Letter (1996) 38, 75-82)

Arrhythmia (Links point to ECGs)	Drug of Choice (Non-drug therapy)	Alternatives (Non-drug therapy)
Atrial fibrillation/flutter	• (Cardioversion) • Verapamil, diltiazem, or beta-blocker to slow ventricular response	• Digoxin to slow ventricular response • Class IA, IC drugs for long-term suppression • Ibutilide for termination • Low dose amiodarone for prevention • Dofetilide for prevention • (RF ablation)
Other supraventricular tachycardias	• Adenosine, verapamil, or diltiazem for termination • (RF ablation)	• Class II drugs or digoxin for termination • (Cardioversion or atrial pacing) • Class IA, IC, II, or IV drugs or digoxin for long-term suppression
PVCs or non-sustained ventricular tachycardia	• No drug therapy for asymptomatic patients	• Class II drugs for symptomatic patients
Sustained ventricular tachycardia	• (Cardioversion or chest thump is the safest and most effective treatment) • Lidocaine for acute treatment	• Procainamide, bretylium or amiodarone for acute treatment • Sotalol, amiodarone, Class IA, IB, II, III can be used for long-term suppression • (RF ablation or ICD)
Ventricular fibrillation	• (Defibrillation is treatment of choice)	• Amiodarone, procainamide or bretylium

	• Lidocaine to prevent recurrence	to prevent recurrence • (RF ablation or ICD)
Digitalis-induced ventricular tachyarrhythmia	• Digibind for life-threatening toxicity	• Lidocaine • Phenytoin • Avoid cardioversion except for ventricular fibrillation • Potassium (if hypokalemic)
Torsades de pointes	• Magnesium sulfate	• Remove causative agents • Isoproterenol • Potassium (if hypokalemic) • (Cardiac pacing)

Table 4. Relative Efficacies of Antiarrhythmic Drugs by Class (Adapted from Melmon and Morelli, 3rd ed.)

Drug Class	Efficacy
IA	Atrial fibrillation Ventricular arrhythmias
IB	Ventricular arrhythmias
IC	AV nodal reentry WPW-related arrhythmias Ventricular arrhythmias (can increase mortality despite suppressing PVCs)
II	Atrial fibrillation/flutter (Ventricular arrhythmias)
III	Atrial fibrillation/flutter Ventricular arrhythmias
IV	Atrial fibrillation/flutter Atrial automaticities

	AV nodal reentry
Adenosine	AV nodal reentry Orthodromic tachycardia
Digitalis	AV nodal reentry Atrial fibrillation/flutter
Magnesium	Torsades de pointes

Table 5. Adverse Extra-Cardiac Effects of Selected Antiarrhythmic Drugs (Adapted from The Medical Letter 33:55-60 and Katzung, 8th ed.)

Drug (Class)	Adverse Extra-Cardiac Effects and Toxicities
Quinidine (IA)	• GI disturbances in 30-50% of patients: diarrhea, nausea, vomiting • Cinchonism • Hypotension (due to alpha-adrenergic blocking activities) • Can elevate serum digoxin concentrations, resulting in digitalis toxicity • Hypersensitivity reactions: rashes, fever, angioneurotic edema, hepatitis • Reversible thrombocytopenia
Procainamide (IA)	• Hypotension (due to ganglionic blocking activity) • Long-term use results in a lupus-like syndrome in 15-30% of patients consisting of arthralgia and arthritis (pleuritis, pericarditis, parenchymal pulmonary disease also occur in some patients) • GI symptoms in 10% of patients • Adverse CNS effects: giddiness, psychosis, depression, hallucinations • Hypersensitivity reactions: fever, agranulocytosis (can lead to fatal infections), Raynaud's syndrome, myalgias, skin rashes, digital vasculitis
Lidocaine (IB)	• **Lowest incidence of toxicity of currently used antiarrhythmic**

	drugs • CNS depression: drowsiness, disorientation, slurred speech, respiratory depression, nausea • CNS stimulation: tinnitus, muscle twitching, psychosis, seizures • Concurrent use of tocainide or mexiletine can cause additive CNS toxicity, including seizures (seizures respond to i.v. diazepam)
Tocainide (IB) **Mexiletine (IB)**	• GI effects: nausea, vomiting • CNS effects: dizziness, disorientation, tremor • Hematological effects (0.2%) with tocainide: agranulocytosis, bone marrow suppression, thrombocytopenia; can lead to death • Concurrent use of either of these drugs and quinidine in combination may be effective at lower doses than either drug alone and thereby minimize adverse effects of both drugs
Flecainide (IC)	• CNS effects in 10-15% of patients: dizziness, tremor, agitation, headache, visual disturbances • GI upset
Amiodarone (III)	• Although this drug is highly effective in treating many arrhythmias, its large number adverse effects limits its clinical use • **Adverse effects are common** (more than 75% of patients receiving drug) and increase after a year of treatment; some toxicities result in death • **Half-life of 25-110 days** can prolong toxicity • Pulmonary toxicity and fibrosis (10-15%, can cause death in 10% of those affected); can be irreversible • Constipation in 20% of patients) • Hepatic dysfunction; can be irreversible • Asymptomatic corneal deposits occur in all patients • CNS effects (ataxia, dizziness, depression, nightmares, hallucinations) • Hypothyroidism or hyperthyroidism (5% of patients)

	• Cutaneous photosensitivity (25% of patients) and blue-grey discoloration of skin (less than 5% of patients) • Peripheral neuropathy • Substantial increases in LDL-cholesterol concentrations often seen; phospholipidosis • Enhances the effect of warfarin and increases the serum concentrations of digoxin, quinidine, procainamide, flecainide, theophylline and other drugs
Digitalis (Misc.)	• Many adverse non-cardiac effects (anorexia, nausea, vomiting, diarrhea, abdominal pain, headache, confusion, abnormal vision) • Adverse effects may indicate digitalis toxicity
Adenosine (Misc.)	• **Short half-life in blood (less than 10 seconds)** • Causes hypotension, flushing in 20% of patients • Transient dyspnea, chest discomfort (non-myocardial) in > 10% • Metallic taste • Headache, hypotension, nausea, paresthesias are less common

Recommended Reading

- Katzung (8th ed.) Chapt. 14 or

- Goodman & Gilman (9th ed.), Chapt. 35

    Supplemental Reading

    o "Antiarrhythmics-from cell to clinic: past, present, and future," Heart 84:14-24 (2000)

    o Symposium Proceedings: "Changing Trends in Antiarrhythmic Therapy," Am. J. Cardiol. (1997) 80(8A):1G-104G

        ▪ "Controlling cardiac arrhythmias: an overview with a historical perspective," Am J Cardiol. (1997) 80(8A): 4G-15G. Review.

    o "Drugs for cardiac arrhythmias," The Medical Letter (1996), 38: 75-82

    o Clinical Pharmacology (Melmon & Morrelli) (3rd ed.) Chapt. 6