Cardiac Arrhythmias and Advanced Cardiac Life Support

Core Therapeutic Module Series

Planned by the ASHP Section of Clinical Specialists and Scientists.

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ACTIVITY FACULTY

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This activity is intended for pharmacy practitioners who are seeking to update their knowledge and skills commensurate with a board certification examination.

ACTIVITY OVERVIEW

The purpose of this activity is to help participants prepare for a Board of Pharmacy Specialty (BPS) examination by providing a review of pertinent topics, practice of required skills, and references to helpful study resources. Faculty will discuss therapeutic management of issues and provide resources on the disease state. The activity will assist the participant identify areas needed for in-depth review.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to:

- Interpret signs, symptoms and diagnostic tests for cardiac arrhythmias.
- Identify drug-related problems, including drug interactions and adverse effects, associated with pharmacotherapy of cardiac arrhythmias.
- Identify and prevent drug-induced cardiac arrhythmias.
- Determine the most appropriate therapy and monitoring for cardiac arrhythmias based on patient-specific information and the most current guidelines.
- Utilize advanced cardiac life support (ACLS) guided therapies.

CONTENT OUTLINE

Antiarrhythmic Drugs: An Overview

I. Mechanism of Action and Classification of the Antiarrhythmic Drugs[1-3]

a. Vaughan-Williams classification: most commonly referred to classification system
   i. Class I: sodium channel antagonists
   ii. Class II: beta-adrenergic receptor antagonists
   iii. Class III: potassium channel antagonists
   iv. Class IV: calcium channel antagonists

b. Physiologic effects
   i. Depress automaticity of abnormal pacemaker cells
   ii. Alter/interfere with reentry pathways
   iii. Terminate premature impulses that trigger reentry
   iv. Decrease the speed (velocity) of conduction

Table 1. Vaughan-Williams Classification, Mechanism of Action, and Utility of the Antiarrhythmic Drugs[1-3]

Vaughn-Williams Classification	Medications	Impact on Conduction Velocity	Impact on Refractory Period	Impact on Automaticity	Ion Channel Affected	Clinical Utility
Ia	Quinidine Procainamide Disopyramide	↓	↑	↓	Na/K	Atrial & ventricular arrhythmias
Ib	Lidocaine Mexiletine	↓	↓	↓	Na (fast)	Ventricular arrhythmias
Ic	Flecainide Propafenone	↓ ↓	0	↓	Na (slow)	Atrial arrhythmias
II	β-adrenergic antagonists	↓	↑	↓	Ca (indirect)	Atrial & ventricular arrhythmias
III	Amiodarone Dofetilide Dronedarone Ibutilide Sotalol	0	↑ ↑	0	K	Atrial & ventricular arrhythmias
IV	Verapamil Diltiazem	↓	↑	↓	Ca (L-type)	Atrial & ventricular arrhythmias

↑ = increases; ↓ = decreases; 0 = no effect; Na = sodium; K = potassium; Ca = calcium

v. Of note, most of the antiarrhythmic drugs are not "pure"—most have multiple mechanisms of action
    1. Amiodarone: displays activity of all antiarrhythmic drug classes
    2. Beta-adrenergic receptor antagonism: disopyramide, propafenone, amiodarone, dronedarone, sotalol

c. Recommended doses of the antiarrhythmic drugs (Tables 2 & 3)[3,4]
    i. In general, dose depends on type of arrhythmia being treated – ventricular arrhythmias generally require higher doses than supraventricular/atrial arrhythmias
    ii. Dose adjustments may be required in some cases for renal and/or hepatic insufficiency
        1. Renal insufficiency: disopyramide, flecainide, sotalol, dofetilide (contraindicated when creatinine clearance less than 20 mL/min)
        2. Hepatic insufficiency: quinidine, disopyramide, lidocaine, mexiletine, flecainide

Table 2. Typical Doses of the Antiarrhythmic Drugs for Intravenous Administration[3,4]

Medication	Loading/Bolus Dose	Maintenance Dose	Conditions Requiring Dose Adjustments
Procainamide	15—18 mg/kg	1—4 mg/min	Renal and hepatic insufficiency
Lidocaine	0.5—1.5 mg/kg; max 3 mg/kg	1—4 mg/min	Hepatic insufficiency, acute heart failure, acute coronary syndrome, shock
Amiodarone	150—300 mg	1 mg/min for 6 hr, then 0.5 mg/min	—
Ibutilide	1 mg; may repeat up to 2 mg	—	—
Sotalol	—	75—150 mg up to q 12 hr	Renal insufficiency

min = minute; hr = hour

Table 3. Typical Maintenance Doses of the Antiarrhythmics Drugs[3,4]

Medication	Typical Maintenance Dose	Conditions Requiring Dose Adjustments
Quinidine	Sulfate: 200—300 mg q 6 hr	Hepatic insufficiency
Disopyramide	100—150 mg q 6 hr 200—300 mg q 12 hr (SR)	Renal and hepatic insufficiency
Mexiletine	200—300 mg q 8 hr	Hepatic insufficiency
Flecainide	50—150 mg q 12 hr	Renal and hepatic insufficiency
Propafenone	150—300 mg q 8 hr 225—425 mg q 12h (ER)	Hepatic insufficiency
Amiodarone	200—400 mg q day	—

Dofetilide	500 mcg q 12 hr	Renal insufficiency
Dronedarone	400 mg q 12 hr	—
Sotalol	80—160 mg q 12 hr	Renal insufficiency

hr = hours; SR = sustained release; ER = extended release

d. Safety of the antiarrhythmic drugs[3,4]
   i. Adverse reactions are exhaustive and extensive, varying from bothersome to life threatening (Table 4)
   ii. Many adverse reactions are consistent within an antiarrhythmic drug class
      1. Class 1a: gastrointestinal intolerance
      2. Class 1b: central nervous system intolerance
   iii. Majority of patients on antiarrhythmic therapy will experience adverse reactions; many will not tolerate long-term therapy

Table 4. Adverse Reactions of the Antiarrhythmic Drugs*[3,4]

Medication	Significant Adverse Reactions
Quinidine	Gastrointestinal intolerance, anorexia, cinchonism†, hypersensitivity reaction resulting in hemolysis and hepatitis, thrombocytopenia,
Procainamide	Drug-induced lupus erythematosus, gastrointestinal intolerance, hepatotoxicity, agranulocytosis
Disopyramide	Anticholingeric syndrome, gastrointestinal intolerance, fatigue, hypoglycemia, hepatic cholestasis, hepatotoxicity, agranulocytosis
Lidocaine	Dizziness, drowsiness, visual disturbances, psychosis, seizures, coma
Mexiletine	Ataxia, tremor, gastrointestinal intolerance, hepatotoxicity, agranulocytosis, drug-induced lupus erythematosus
Flecainide	Dizziness, photopsia, blurred vision, dizziness, corneal deposits, gastrointestinal intolerance
Propafenone	Gastrointestinal intolerance, dizziness, dyspnea, fatigue, drug-induced lupus erythematosus, agranulocytosis
Amiodarone	Photophobia, blurred vision, corneal deposits, photosensitivity, ataxia, parasthesias, gastrointestinal intolerance, hepatoxicity, hyper-/hypothyroidism, pulmonary fibrosis
Dofetilide	Dizziness, headache, angina
Dronedarone	Increased serum creatinine, gastrointestinal intolerance, asthenia, rash, hepatotoxicity
Ibutilide	Nausea, headache
Sotalol	Fatigue, dizziness, palpitations, dyspnea, headache

*This table is not all inclusive, but represents major adverse reactions reported relevant to each medication.

†Cinchonism: flushing, sweating, tinnitus, blurred vision, impaired hearing, confusion, headache, and dizziness; in severe forms can cause deafness, blindness, and death.

iv. In addition to these adverse reactions, the antiarrhythmic drugs are *pro*arrhythmic
    1. Proarrhythmia: onset of a new arrhythmia
    2. Examples: atrioventricular (AV) block, Torsades de Pointes

e. Monitoring parameters[3,4]
    i. Extensive monitoring is generally required due to narrow therapeutic index and propensity for serious adverse reactions
    ii. For any antiarrhythmic drug, monitoring parameters should include:
        1. Consideration for adverse reactions
        2. Electrocardiogram (ECG)
        3. Blood pressure
        4. Heart rate
    iii. Individualized monitoring plan should be developed for each patient based on the antiarrhythmic drug utilized, including, in general:
        1. Quinidine: complete blood count (CBC), liver function tests (LFTs)
        2. Procainamide: antinuclear antibody (ANA), CBC, LFTs, symptoms of heart failure/exacerbation
        3. Disopyramide: glucose, CBC, LFTs, symptoms of heart failure/exacerbation
        4. Lidocaine: therapeutic concentration in patients unable to report central nervous system effects
        5. Mexiletine: ANA, CBC, LFTs
        6. Flecainide: LFTs, ophthalmologic examination, serum creatinine, symptoms of heart failure/exacerbation
        7. Propafenone: ANA, CBC, symptoms of heart failure/exacerbation
        8. Amiodarone: LFTs, thyroid function tests (TSH), serum creatinine, chest radiograph (x-ray), ophthalmologic examination, pulmonary function tests, serum electrolytes
        9. Dronedarone: LFTs, serum creatinine
        10. Dofetilide: serum creatinine, serum electrolytes
        11. Sotalol: serum creatinine, serum potassium and magnesium, symptoms of heart failure/exacerbation
    iv. Therapeutic drug monitoring is available for most antiarrhythmic drugs, although clinical utility for most is unknown
        1. Amiodarone: 0.5-2.5 mcg/mL
        2. Disopyramide: 2.8-3.2 mcg/mL (atrial arrhythmias); 3.3-7.5 mcg/mL (ventricular arrhythmias)
        3. Flecainide: 0.2-1 mcg/mL
        4. Lidocaine: 1.5-5 mcg/mL
        5. Mexiletine: 0.5-2 mcg/mL
        6. Procainamide: 4-10 mcg/mL
        7. Quinidine: 2-5 mcg/mL

f. Antiarrhythmic drug-drug interactions[4-6]
    i. Drug interactions are extensive and often clinically significant
    ii. Many of the antiarrhythmic drugs are substrates of cytochrome (CYP) P450 enzymatic pathways (Table 5)
    iii. Of particular concern are the interactions with other cardiovascular medications (Table 6)

iv. Additional mechanism of antiarrhythmic drug interactions:
    1. Inhibition of p-glycoprotein: quinidine
    2. Renal cation transport system: dofetilide (contraindicated with cimetidine, trimethoprim, ketoconazole, megestrol, prochlorperazine)
    3. Pharmacodynamic interactions
        a. Additive beta-blockade: disopyramide, propafenone, amiodarone, dronedarone, sotalol
        b. Proarrhythmia as a result of electrolyte wasting: dofetilide, amiodarone

Table 5. Metabolic Activity of the Antiarrhythmic Drugs[4-6]

CYP P450 Enzyme	Substrate	Inhibitor
CYP 1A2	Lidocaine Mexiletine Propafenone	Lidocaine Mexiletine
CYP 2C9	—	Amiodarone
CYP 2D6	Flecainide Mexiletine Propafenone Dronedarone	Amiodarone Dronedarone Flecainide Propafenone Quinidine
CYP 3A4	Amiodarone Dronedarone Disopyramide Lidocaine Propafenone Quinidine	Quinidine Amiodarone Dronedarone

Table 6. Antiarrhythmic Drug Interactions with Other Cardiovascular Medications[4-6]

Antiarrhythmic Drug	Other Cardiovascular Medications*
Amiodarone	Apixaban, Atorvastatin, Beta-adrenergic receptor antagonists, Clopidogrel, Dabigatran, Digoxin, Diltiazem, Fluvastatin, Irbesartan, Losartan, Rivaroxaban, Simvastatin, Torsemide, Vasopressin, Verapamil, Warfarin
Dofetilide	Diuretics, Hydrochlorothiazide, Ranolazine, Triamterene, Vasopressin, Verapamil
Dronedarone	Apixaban, Atorvastatin, Beta-adrenergic receptor antagonists, Dabigatran, Digoxin, Diltiazem, Lovastatin, Nifedipine, Simvastatin, Torsemide, Verapamil, Warfarin
Propafenone	Metoprolol, Ranolazine, Propranolol, Vasopressin, Warfarin
Quinidine	Aspirin, Atenolol, Diltiazem, Digoxin, Metoprolol, Nifedipine, Propranolol, Ranolazine, Rivaroxaban, Vasopressin, Verapamil, Warfarin
Sotalol	Beta-Blockers, Clonidine, Digoxin, Diltiazem, Diuretics, Ranolazine, Vasopressin, Verapamil

*This chart is for illustrative purposes and is not meant to be all-inclusive

g. Antiarrhythmic drug therapeutic decision making
    i. Selecting the optimal antiarrhythmic drug is a complex decision making process
    ii. When selecting an antiarrhythmic agent, must consider:
        1. Co-morbid disease states, especially cardiovascular disorders
        2. Concomitant medications and potential for drug interactions
        3. Patient's previous experience with antiarrhythmic therapy
        4. Requirements related to monitoring parameters

Supraventricular Arrhythmias: An Overview

I. Classification and Characterization of Supraventricular Cardiac Arrhythmias[7,8]

a. Classification based upon location and/or structures involved

b. Supraventricular arrhythmias: arrhythmias that occur "above" the ventricles

i. Generally requires the atrium and/or AV node to be involved; often referred to as "atrial arrhythmias"

ii. Results from increased automaticity and/or re-entry pathways

iii. Vary extensively in clinical presentation, occurrence, risk, and severity (Tables 7 & 8)

iv. Includes:

1. Supraventricular tachycardia
2. Atrial tachycardia
3. Atrial fibrillation and flutter
4. Sinus arrhythmias
5. Wandering atrial pacemaker

Table 7. Clinical Presentation of the Supraventricular Arrhythmias[7]

Objective	Subjective
Tachypnea	Dyspnea
Tachycardia	Fatigue, weakness
Labile blood pressure	Dizziness
Hypotension	Angina, chest "pressure"
Altered mental status	Palpitations
Hemodynamic instability	Syncope, presyncope
Electrocardiogram (ECG) Abnormalities	Confusion

Table 8. Precipitating Factors for Supraventricular Arrhythmias[7]

Cardiac Factors	Non-Cardiac Factors
Coronary artery disease	Stimulants (e.g., nicotine, caffeine)
Myocardial infarction	Alcohol
Valvular disease	Hyperthyroidism
Cardiomyopathy	Medications (e.g., antiarrhythmic drugs, antibiotics, antihistamines)
Heart failure	Infection, fever
Congenital heart disease	Electrolyte disturbances (e.g., potassium, magnesium)

II. Paroxysmal supraventricular tachycardia (SVT)[7,8]
    a. Definition: arrhythmia associated with reentry pathway – either AV nodal, SA nodal, or intra-atrial reentry; characterized as a narrow QRS complex tachycardia with heart rate greater than 150 bpm (in adults)

    b. Acute management based on hemodynamic parameters: is the patient stable or unstable?
        i. Unstable generally defined as impaired organ function and/or cardiac arrest is imminent
        ii. Signs of instability: hypotension, altered mental status, shock, ischemic ECG changes, heart failure
        iii. Must determine if instability is direct result of tachycardia

    c. If unstable[4,8,9]:
        i. Adenosine
            1. Drug of choice for SVT
            2. Mechanism of action: slows SA and AV node conduction and interrupts AV nodal reentry pathways → think "Ctrl + Alt + Delete"
            3. Extremely short half-life ≈ 6 seconds
            4. Dose: 6 mg rapid IV bolus followed by rapid administration of minimum of 20 mL normal saline; may repeat as needed in 1—2 minutes with 12 mg x 2 doses up to 30 mg total
            5. 80-90% of patients in SVT will convert to sinus rhythm within 5 minutes
            6. Avoid in patients with 2nd- or 3rd-degree AV block or sinus node disease and in patients with bronchoconstriction/spasm (i.e., asthma)
            7. Significant drug interactions of note: dose reduction to 3 mg required in patients taking dipyridamole or carbamazepine; increased doses may be required in patients on theophylline or with excessive caffeine intake
            8. Notable adverse reactions:
                a. Flushing, dyspnea, chest pressure, asystole may appear on ECG
                b. Adverse reactions are pronounced but transient and warrant patient counseling
        ii. Synchronized cardioversion
            1. Cardioversion must be synchronized to the QRS complex; failure to do would result in defibrillation, which may result in ventricular arrhythmias including ventricular fibrillation
            2. Sedation should be administered to all conscious patients whenever possible
            3. Recommended dose: 50—100 Joules

    d. If stable, non-pharmacologic measures may be attempted first, followed by pharmacologic intervention if unsuccessful[7-9]
        i. Non-pharmacologic measures:

1. Vagal maneuvers successfully convert up ≈ 25%
2. Carotid massage generally not recommended

ii. Pharmacologic treatment options
1. Adenosine (see above)
2. Beta-adrenergic receptor antagonists: slow AV node conduction, negative inotropic effect
    a. Metoprolol 5 mg IV; may repeat up to total of 3 doses (15 mg)
    b. Esmolol 500 mcg/kg IV loading dose followed by 50 mcg/kg/minute; titrate to response by administering subsequent loading doses and increasing titration to max dose of 200 mcg/kg/minute
3. Calcium channel antagonists: slow AV node conduction, terminate reentry pathways
    a. Verapamil 2.5—5 mg IV; may repeat up to total 20 mg
    b. Diltiazem 0.25 mg/kg IV bolus (average 15—20 mg); may repeat with 0.35 mg/kg IV (20—25 mg); follow with 5—15 mg/hour infusion
4. Antiarrhythmic drugs
    a. Generally consider last-line due to delayed onset of action, toxicity, and risk for proarrhythmia
    b. May be preferentially considered in setting of acute heart failure or in presence of contraindications to beta-adrenergic receptor antagonists or calcium channel antagonists
    c. Preferred: amiodarone 150 mg IV over 10 minutes (may repeat x 1) followed by continuous infusion 1 mg/minute for 6 hours followed by 0.5 mg/min to maximum dose 2.2 grams

e. Monitoring parameters: blood pressure, heart rate, symptom resolution, ECG (arrhythmia recurrence, proarrhythmia), assess need for long-acting medication after initial stabilization

f. Identify and treat any reversible causes

Table 9. Causes of SVT[7,8]

Cardiac Causes	Non-Cardiac Causes
Coronary artery disease Myocardial infarction Heart failure Cardiomyopathy	Stimulants – nicotine, caffeine Alcohol Hyperthyroidism Anemia Fever, Infection

g. Chronic management of SVT[7]
    i. Long-term/preventative therapy generally not required
    ii. Preventative therapy is indicated if patient experiences:
        1. Frequent episodes occur that require intervention
        2. Infrequent episodes that are severely symptomatic
    iii. Preventative therapy options
        1. AV nodal blocking agents (beta-adrenergic receptor antagonists or calcium channel antagonists)
        2. Antiarrhythmics: class 1c antiarrhythmic drugs preferred (flecainide and propafenone)
    iv. Transcutaneous catheter ablation may be considered in some patients

III. Atrial flutter[7,10]
    a. Definition: narrow complex arrhythmia characterized by "saw tooth" pattern on ECG; often associated with rapid ventricular rate
        i. Atrial contraction ≈ 300 beats per minutes (bpm)
        ii. AV conduction to ventricles often 2:1, resulting in a heart rate of 150 bpm

    b. Occurs in approximately 25-35% of patients with atrial fibrillation

    c. Often (≈60%) presents as part of an acute disease process (e.g., infection)

    d. Often associated with intense symptoms—palpitations, dyspnea, fatigue, angina

    e. Acute management based on hemodynamic parameters: is the patient stable or unstable?

    f. If patient is unstable, consider synchronized cardioversion (50—100 Joules)

    g. If patient is stable:
        i. Attempt to control ventricular rate with AV-nodal blocking agents (e.g., beta-adrenergic receptor antagonists or calcium channel antagonists)
        ii. If pharmacologic control ineffective, consider non-pharmacologic measures (e.g., synchronized cardioversion, atrial pacing)

    h. Chronic management
        i. Chronic therapy often not needed if acute disease process is controlled
        ii. Treatment recommendations are based upon recommendations available for atrial fibrillation, as research and guidelines do not distinguish as separate treatment groups
        iii. Catheter ablation may be required

IV. Atrial Fibrillation[10-24]

a. Epidemiology[10,11]

i. Most common sustained cardiac arrhythmia

1. Prevalence: estimates range from 2.7 million up to 6.1 million cases in the United States; ≈33.5 million cases worldwide
2. Prevalence higher in men, Caucasians, and with increasing age

ii. Prevalence expected to increase at a rate greater than projected; attributed to overall increased life expectancy and decreased mortality from cardiovascular disease

b. Pathophysiology[10]

i. Atria fibrillate, resulting in loss of organized atrial contraction
ii. Classic ECG findings show irregularly irregular rhythm, no definable p waves and variable ventricular response (variable R—R interval)
iii. Ventricular response dependent on AV node to serve as a "filter;" can be slow, normal, or fast

c. Classification based on length and number of episodes

i. Acute vs. chronic
ii. Paroxysmal: terminates spontaneously within 7 days of onset
iii. Persistent: persists greater than 7 days
iv. Long-standing persistent: persists greater than 12 months
v. Permanent

d. Causes[10,11]

i. Often associated with underlying cardiac disease: heart failure, coronary artery disease, hypertension, valvular heart disease
ii. Associated with several other co-morbid conditions: obesity, diabetes, hyperthyroidism, chronic kidney disease, sleep apnea, advancing age
iii. May be associated with reversible causes: surgery, pulmonary embolism, infection, myocardial infarction

e. Clinical outcomes and prognosis: associated with increased long-term risk of[7,8,10-24]:

i. Rapid ventricular response

1. Ventricular response dependent on AV node to serve as a "filter"
2. Inadequacy of the "filter" can result in a rapid ventricular response (i.e., tachycardia), potentially resulting in hemodynamic instability

ii. Heart failure

1. Complex, bi-directional relationship: heart failure promotes atrial fibrillation while atrial fibrillation may exacerbate heart failure
2. Dual diagnosis associated with poor prognosis

iii. Stroke[10-24]

1. Independent risk factor for stroke, increasing risk ≈ 5 fold
2. Rate of ischemic stroke ≈5-6% *per year*
3. Diagnosed/undiagnosed strokes + transient ischemic attacks ≈>7% *per year*
4. Pathophysiology of stroke in atrial fibrillation three-fold[12]:
    a. Blood stagnation in the left atrium and left atrial appendage as a result of ineffective contraction leads to thrombus formation
    b. Atrial fibrillation is associated with an increase in several prothrombotic markers → hypercoagulable state
    c. Numerous structural changes occur in the atria, resulting in endothelial and endocardial damage
5. Risk for stroke remains in patients with asymptomatic atrial fibrillation and paroxysmal atrial fibrillation
6. Risk stratification tool: CHA_2DS_2-VASc score[10]
    a. As CHA_2DS_2-VASc score increases, risk for stroke increases
    b. Adjusted annual stroke rate based on CHA_2DS_2-VASc score (% per year)
        i. CHA_2DS_2-VASc score 1 = 1.3%
        ii. CHA_2DS_2-VASc score 2 = 2.2%
        iii. CHA_2DS_2-VASc score 4 = 4.0%
        iv. CHA_2DS_2-VASc score 6 = 9.8%
        v. CHA_2DS_2-VASc score 9 = 15.2%

Table 10. CHA_2DS_2-VASc Score for Risk Stratification of Stroke in Nonvalvular Atrial Fibrillation[10]

CHA_2DS_2-VASc Criteria	Risk Score
*C*ongestive heart failure	1 point
*H*ypertension	1 point
*A*ge 75 years or greater	2 points
*D*iabetes mellitus	1 point
*S*troke, TIA, or Thromboemoblism (prior)	2 points
*V*ascular disease*	1 point
*A*ge 65—74 years	1 point
*S*ex *c*ategory (i.e., female gender)	1 point

TIA = transient ischemic attack

*Vascular disease includes prior myocardial infarction, peripheral artery disease, or aortic plaque

iv. Mortality[11]
    1. More than double that of sinus rhythm from Framingham studies
    2. Associated with increased risk of sudden cardiac death

f. Management of atrial fibrillation[8,10-24]
    i. Long-term management consists of rate control, rhythm control, and stroke prevention
        1. Rate control: focus on controlling ventricular rate with no regard to rhythm
        2. Rhythm control: attempt to restore and maintain normal sinus rhythm
        3. No survival benefit associated with the rhythm control over rate control
    ii. Treatment strategy should consider:
        1. Type and duration of atrial fibrillation
        2. Type and severity of symptoms
        3. Patient age
        4. Co-morbid conditions/disease states
        5. Short- and long-term treatment goals
        6. Therapeutic options (pharmacological and non-pharmacologic)
    iii. Specific treatment decision must weight risk and benefits of therapy, regardless of the treatment considered and goal being targeted

Table 11. Treatment Considerations for Selecting Rate Control or Rhythm Control Strategy[10]

Favors Rate Control	Favors Rhythm Control
Persistent AF	Initial episode of AF
Permanent AF	Symptomatic AF
Asymptomatic/few symptoms	Frequent hospitalization
Age greater than 65 years	Failure on rate control
Hypertension	Age less than 65 years
Failure of AAD	No hypertension
Patient preference	Patient preference

AF = atrial fibrillation; AAD = antiarrhythmic drug

g. Rate control in atrial fibrillation[10]
    i. Acute rate control is needed in the setting of rapid ventricular response
        1. Rapid ventricular response results in decreased cardiac output
        2. Treatment dependent upon patient response to tachycardia: is the patient symptomatic? Hemodynamically stable?
        3. Treatments goals:
            a. Focus 1: prevent hemodynamic instability and further clinical deterioration associated with uncontrolled rate
            b. Focus 2: improve symptoms

c. Focus 3: avoid cardiac remodeling associated with tachycardia

Table 12. Treatment Considerations for Atrial Fibrillation with Rapid Ventricular Response[8,10]

Symptomatic?	Hemodynamically Stable?	Initial Treatment Recommendation
No	Yes	AV-node blocking agents*; oral route
Yes	Yes	AV-node blocking agents; intravenous route
Yes	No	Direct current cardioversion

* Beta-adrenergic receptor antagonists or calcium channel antagonists

Table 13. Treatment Options for Atrial Fibrillation with Rapid Ventricular Response[10]

Medication	Initial Dose	Repeat Dose(s)	Considerations
Amiodarone	150 mg IV	0.5—1 mg/min	Preferred in patients with acute heart failure
Diltiazem	0.25 mg/kg IV	5—15 mg/hour	↓ BP; Caution in HF
Verapamil	0.075—0.15 mg/kg IV	NA	↓ BP; Caution in HF
Esmolol	500 mcg/kg IV	50—200 mcg/kg/min	↓ BP; Caution in HF, asthma
Metoprolol	2.5—5 mg IV	May repeat to total of 3 doses (15 mg)	↓ BP; Caution in HF, asthma

BP = blood pressure; HF = heart failure; IV = intravenous

4. Beta-adrenergic receptor antagonists or calcium channel antagonists preferred for acute rate control
5. Digoxin not recommended for acute, immediate rate control
6. Monitoring parameters
    a. Safety: blood pressure, heart rate, ECG, adverse reactions
    b. Efficacy: symptom control, blood pressure, heart rate

ii. Long term rate control
    1. Treatment goals:
        a. Goal resting heart rate < 80 bpm for symptom control
        b. Lenient rate < 110 bpm may be appropriate for patients if asymptomatic and preserved left ventricular systolic function
    2. Beta-adrenergic receptor antagonists most effective for rate control
    3. Nondihydropyridine calcium channel antagonists may be considered as alternative
    4. Digoxin or amiodarone may be considered as last line options or when beta-adrenergic receptor antagonists or calcium channel antagonists are contraindicated
    5. Dronedarone should *not* be used for rate control in patients with permanent atrial fibrillation
    6. Some patients may require combination therapy for optimal rate control
    7. Monitoring parameters:
        a. Safety: blood pressure, heart rate, ECG, adverse reactions
        b. Efficacy: heart rate, exercise tolerance, ECG, symptom control
    8. AV nodal ablation with ventricular pacing may be considered when rate control is inadequate/refractory and when rhythm control cannot be achieved

iii. Rhythm control[8,10]
    1. Acute rhythm control → cardioversion
        a. May be accomplished utilizing either synchronized direct current cardioversion or antiarrhythmic drugs (i.e., pharmacologic cardioversion)
            i. Synchronized direct current cardioversion should be utilized in hemodynamically unstable patients
            ii. Pharmacologic cardioversion most effective if within 7 days of onset; generally less effective than synchronized cardioversion
            iii. Pharmacologic cardioversion carries additional risk for proarrhythmia
        b. Options for pharmacologic cardioversion:
            i. Flecainide
            ii. Dofetilide
            iii. Propafenone
            iv. Ibutilide
            v. Amiodarone
        c. Quinidine or procainamide may be considered, although level of evidence not well established
        d. Digoxin and sotalol should not be used for acute cardioversion

2. Stroke prevention during acute cardioversion
    a. Acute cardioversion associated with increased risk for stroke; risk highest when atrial fibrillation present ≥ 48 hours
    b. All patients should be assessed for need for anticoagulation based on duration of atrial fibrillation (Table 14)
    c. For patients with duration > 48 hours or unknown, transesophageal echocardiogram can be used to evaluate for thrombus
    d. When emergent cardioversion is needed (e.g., hemodynamic instability), anticoagulation should not delay cardioversion but should be followed by at least 4 weeks of anticoagulation

Table 14. Anticoagulation Recommendations for Acute Cardioversion of Atrial Fibrillation[10,13]

Duration of Atrial Fibrillation	Anticoagulation Recommendation*
Less than 48 hours	Begin anticoagulation immediately and for at least 4 weeks after†
Greater than 48 hours	Administer anticoagulation 3 weeks prior to and at least 4 weeks after
Unknown	Administer anticoagulation 3 weeks prior to and at least 4 weeks after

*Anticoagulation = either dose-adjusted warfarin to INR 2—3, low molecular-weight heparin or heparin at treatment doses, or factor Xa or direct thrombin inhibitor

†Consideration for long-term anticoagulation should be given to CHA_2DS_2-VASc score

3. Chronic rhythm control: maintenance of sinus rhythm
    a. Several antiarrhythmic drugs are efficacious for maintaining sinus rhythm after cardioversion
    b. Reversible causes of atrial fibrillation should be ruled out/treated prior to initiating antiarrhythmic drug
    c. Therapeutic decision based on patient-specific variables related to safety of antiarrhythmic drug (Table 15)

Table 15. Therapeutic Recommendations for Maintenance of Sinus Rhythm in Atrial Fibrillation[4,10]

Co-Morbid Condition	Antiarrhythmic Drug(s) of Choice	Alternative Agents
No underlying CV disease	Dronedarone, Flecainide, Propafenone, Sotalol	Amiodarone, Dofetilide
Hypertension, No LVH	Dronedarone, Flecainide, Propafenone, Sotalol	Amiodarone, Dofetilide
Hypertension with LVH	Amiodarone	
Coronary artery disease	Dofetilide, Dronedarone, Sotalol	Amiodarone
Heart failure	Amiodarone, Dofetilide	

CV = cardiovascular; LVH = left ventricular hypertrophy

d. Amiodarone more effective than the Class I antiarrhythmic drugs or sotalol for maintenance of sinus rhythm → however, due to toxicity, generally considered 2nd line
e. Recommendations for initiation of antiarrhythmic drug therapy based on risk for proarrhythmia
    i. Appropriate to initiate as out-patient: amiodarone
    ii. Appropriate to initiate in carefully selected out-patients: sotalol
    iii. Initiate only while hospitalized: dofetilide, procainamide, quinidine, sotalol (if not candidate for out-patient initiation)
f. "Pill in the Pocket" approach to rhythm control
    i. Patient takes single dose of an antiarrhythmic drug when atrial fibrillation symptoms are present
    ii. Antiarrhythmic drug options: propafenone or flecainide
    iii. A beta-blocker or calcium channel blocker should be administered prior to taking the antiarrhythmic drug to prevent rapid ventricular response
    iv. Most patients must be observed/monitored during first attempt before using as out-patient
g. Monitoring parameters
    i. Refer to antiarrhythmic drug section for specific monitoring parameters for individual antiarrhythmic drugs
    ii. Safety: Blood pressure, heart rate, ECG, adverse reactions
    iii. Efficacy: ECG, symptom control

iv. Stroke prevention in atrial fibrillation[10-24]
    1. Recommendations for stroke prevention based upon individual risk assessment using CHA_2DS_2-VASc score (Table 16)
    2. When oral anticoagulation is recommended, warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban may be used

Table 16. Risk Stratification and Recommendation for Stroke Prevention in Nonvalvular Atrial Fibrillation[10]

CHA_2DS_2-VASc Score	Recommendation
0	No therapy recommended
1	Oral anticoagulation, aspirin, or no therapy may be considered
2+	Oral anticoagulation
Any score with previous stroke or TIA	Oral anticoagulation

3. Must consider risk of stroke versus risk of bleeding when selecting therapy
    a. HAS-BLED score may be used to identify patients at increased risk for bleeding
    b. Increased HAS-BLED score associated with increased risk for major bleeding
        i. HAS-BLED score 0 = 0.9%
        ii. HAS-BLED score 1 = 3.4%
        iii. HAS-BLED score 2 = 4.1%
        iv. HAS-BLED score 3 = 5.8%
        v. HAS-BLED score 4 = 8.9%
        vi. HAS-BLED score 5 = 9.1%
    c. Application of HAS-BLED score to clinical decision making still undetermined

Table 17. HAS-BLED Score to Identify Patients at Increased Risk of Bleeding on Anticoagulation[10,17,18]

HAS-BLED Criteria	Risk Score
*H*ypertension (systolic blood pressure >160 mmHg)	1 point
*A*bnormal liver or renal function	1 point each (maximum 2)
*S*troke (history of)	1 point
*B*leeding (history of or predisposition/anemia)	1 point
*L*abile INRs*	1 point
*E*lderly age (>65 years)	1 point
*D*rugs† that promote bleeding or alcohol excess	1 point each (maximum 2)

*Time in therapeutic range < 60%

†Non-steroidal anti-inflammatory drugs, antiplatelet agents and/or steroids

4. Dabigatran[19,20]
    a. Direct thrombin inhibitor
    b. Demonstrated lower rate of stroke (ischemic and hemorrhagic) compared to warfarin with lower rate of minor and major bleeding with exception of major gastrointestinal bleeding, which was significantly higher with dabigatran (150 mg dose)
    c. Recommended dose: 150 mg twice daily
    d. Dose adjustments:
        i. Creatinine clearance 15—30 mL/min: 75 mg twice daily
        ii. Creatinine clearance 30—50 mL/min and on dronedarone or ketoconazole: 75 mg twice daily
    e. Do not use if creatinine clearance <15 mL/min or on dialysis; do not use if creatinine clearance < 30 mL/min with concomitant use of P-glycoprotein inhibitor
    f. Cannot be used in patients with mechanical heart valves (contraindicated)

5. Rivaroxaban[21,22]
    a. Factor Xa inhibitor

   b. Demonstrated non-inferiority for ischemic stroke prevention compared to warfarin with similar rate of major and non-major bleeding
      i. Major gastrointestinal bleeding and need for transfusion higher in rivaroxaban group
      ii. Intracranial hemorrhage lower in rivaroxaban group
   c. Recommended dose: 20 mg once daily with evening meal
   d. Dose adjustments:
      i. Creatinine clearance 15—50 mL/min: 15 mg once daily
   e. Do not use if creatinine clearance < 15 mL/min and/or acute renal failure
   f. Avoid in patients with moderate or severe hepatic impairment
   g. Avoid in combination with strong CYP3A4 and P-glycoprotein inhibitors (e.g., ketoconazole, ritonavir) or inducers (e.g., carbamazepine, rifampin)
   h. Avoid in patients with mechanical heart valves

6. Apixaban[23,24]
   a. Direct factor Xa inhibitor
   b. Demonstrated superiority over warfarin for combined ischemic and hemorrhagic stroke prevention with lower rate of bleeding
      i. Decreased rate of hemorrhagic stroke; non-significant difference in rate of ischemic stroke
   c. Recommended dose: 5 mg twice daily
   d. Dose adjustments:
      i. Reduce to 2.5 mg twice daily if 2 of the following: age ≥ 80 years, body weight ≤60 kg, and/or serum creatinine ≥1.5 mg/dL
      ii. Reduce to 2.5 mg twice daily if receiving stroke dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, ritonavir, clarithromycin)
      iii. Hemodialysis: 5 mg twice daily; reduce to 2.5 mg twice daily if age ≥ 80 years or body weight ≤60 kg
   e. Avoid in patients with moderate to severe hepatic impairment
   f. Avoid use in combination with dual inhibitors of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin)

7. Edoxaban[25,26]
   a. Direct factor Xa inhibitor
   b. Demonstrated non-inferiority for ischemic stroke prevention compared to warfarin with lower rate of major and non-major

bleeding with exception of major gastrointestinal bleeding which was higher in edoxaban group (60 mg dose)

c. Recommended dose: 60 mg once daily
d. Dose adjustments:
    i. Creatinine clearance 15—50 mL/min: 30 mg once daily
e. Do not use in patients with creatinine clearance greater than 95 mL/min due to increased rate of ischemic stroke
f. Do not use if creatinine clearance less than 15 mL/min
g. Avoid in patients with moderate or severe hepatic impairment
h. Avoid use in combination with p-glycoprotein inhibitors (rifampin)

8. Dose-adjusted warfarin (target INR 2.5, goal 2—3) should be used over other anticoagulants in patients:
    a. With mechanical heart valves (INR goal may be 2.5—3.5 depending on type and location of valve)
    b. With mitral stenosis
    c. At extremes of weight (e.g., greater than 120 or less than 60 kg)

9. Warfarin may be continued in patients who are:
    a. Well controlled on current regimen
    b. "Satisfied with [current regimen]"
    c. Unlikely to be adherent or do not desire twice daily dosing

10. Selection of anticoagulant based on patient-specific factors: co-morbid conditions, patient preference, previous experience on anticoagulants, potential for drug interactions, cost

11. Instructions for converting from one anticoagulant to another available in prescribing information
    a. Dabigatran → Warfarin: stop warfarin, start when INR less than 2.0
    b. Rivaroxaban → Warfarin: stop warfarin, start when INR less than 3.0
    c. Apixaban → Warfarin: stop warfarin, start when INR less than 2.0
    d. Edoxaban → Warfarin: stop warfarin, start when INR less than/equal to 2.5

12. Monitoring parameters:
    a. Safety: INR (dose-adjusted warfarin), bleeding, hospitalization, adverse reactions, renal function
    b. Efficacy: INR (dose-adjusted warfarin), hospitalization, new stroke onset

Ventricular Arrhythmias: An Overview

I. Pathophysiology, Epidemiology, and Clinical Presentation of the Ventricular Arrhythmias[27]

a. Represent arrhythmias with foci in and/or affecting the ventricles

b. Vary extensively in clinical presentation, from benign to life-threatening (Table 17)

c. Includes:

i. Premature ventricular contractions
ii. Non-sustained or sustained ventricular tachycardia
iii. Ventricular fibrillation
iv. Torsades de Pointes

Table 18. Clinical Presentation of the Ventricular Arrhythmias[27]

Objective	Subjective
Tachypnea	Dyspnea
Tachycardia	Fatigue, weakness
Labile blood pressure	Dizziness
Hypotension	Angina
Altered mental status	Chest “pressure”
Hemodynamic instability	Palpitations
Electrocardiogram (ECG) Abnormalities	Syncope, presyncope
Sudden cardiac death	Confusion

d. Risk factors for ventricular arrhythmias[27]:

i. Underlying cardiovascular disease: coronary artery disease, left ventricular hypertrophy, cardiomyopathy, hypertension, hyperlipidemia, long QT syndrome, Brugada Syndrome
ii. Other risk factors: tobacco abuse, illicit drug abuse, obesity, diabetes, genetic influence/disposition

II. Management of Ventricular Arrhythmias[27]

a. Premature Ventricular Contractions (PVCs)[27]

i. Ventricular depolarization that occurs spontaneously and independent of the AV node
ii. Clinical presentation: typically asymptomatic; may be associated with intermittent chest pain or pressure
iii. Clinical significance varies from benign to being associated with increased risk for sudden cardiac death

1. Relatively frequent occurrence on ECG; in otherwise healthy patients, infrequent PVCs at rest are typically benign

2. Frequent PVCs in patients with underlying cardiovascular disease may imply increased risk
3. PVCs that occur during exercise may imply increased risk
4. Frequent or repetitive PVCs (greater than 10 PVCs per hour) in post-myocardial infarction patients implies increased risk

iv. Management
1. Currently no treatment warranted for PVCs
2. Serves as a marker to warrant further cardiovascular investigation and risk mitigation strategies

b. Ventricular tachycardia and ventricular fibrillation[8,27]

i. Ventricular tachycardia: defined as three or more consecutive beats arising from the ventricles at a rate greater than 100 bpm
1. Non-sustained ventricular tachycardia – terminates spontaneously < 30 seconds
2. Sustained ventricular tachycardia – persists > 30 seconds or requires intervention to terminate due to instability and/or clinical deterioration
3. Also classified based on presence or absence of pulse
4. Acute onset considered medical emergency – patients with an initial pulse may quickly deteriorate to cardiac arrest if left untreated

ii. Ventricular fibrillation: disordered, unsynchronized, rapid fibrillation of the ventricles
1. Associated with immediate loss of cardiac output
2. Most common cause of sudden cardiac death
3. Associated with grim prognosis; ≈10% increase in mortality for every 1 minute in ventricular fibrillation

iii. Acute care and long-term treatment strategies are the same, regardless of whether ventricular tachycardia or fibrillation

iv. Acute management: see section on advanced cardiac life support (below)

v. Long term management[27-30]
1. Long term management is focused on secondary prevention
a. Identify underlying cause and/or risk factors
b. Target risk management strategies for underlying risk factors (e.g., hypertension, hyperlipidemia, coronary artery disease)
2. Future arrhythmias are prevented either by implantable cardiac defibrillators (ICDs) and/or antiarrhythmic drugs
3. ICDs have been show to improve survival when compared to antiarrhythmic drug therapy

4. Antiarrhythmic drug therapy
    a. Antiarrhythmic drugs were associated with increased risk of death when evaluated for suppression of ventricular ectopy after acute myocardial infarction
    b. Antiarrhythmic drugs may be considered in select patients as secondary prevention of ventricular arrhythmias—but likely only in combination with an ICD
    c. Amiodarone and sotalol are recommended antiarrhythmic drugs when used in combination with an ICD
5. Combination therapy with an ICD and an antiarrhythmic drug are warranted:
    a. To reduce the frequency of ICD discharge
    b. To reduce the rate of ventricular tachycardia to allow ICD pacing to be effective
    c. To reduce the rate of ICD discharge due to supraventricular tachycardia
    d. To reduce the defibrillation threshold (the amount of ICD energy required for arrhythmia termination)
6. Risks associated with combination ICD/antiarrhythmic drug therapy require careful consideration
    a. Antiarrhythmic drugs pose the risk for proarrhythmia, which would thereby potentially increase the rate of ICD discharge
    b. Antiarrhythmic drugs may slow or change the morphology of ventricular tachycardia to a point that it is undetectable to the ICD
    c. Some antiarrhythmic drugs increase the defibrillation threshold, requiring adjustment to ICD settings and an increase in the energy required for successful arrhythmia termination

vi. Monitoring parameters:
1. Safety: ECG, heart rate, patient report of symptoms, frequency of ICD discharge, adverse reactions/events
2. Efficacy: ECG, frequency of ICD discharge, patient report of symptoms, hospitalization
3. Refer to section on antiarrhythmic drug section for specific monitoring recommendations

III. Medication-Induced Arrhythmias[30-32]
a. Several medications are associated with development of arrhythmias

b. Of particular concern is propensity to prolong the QT interval and/or cause Torsades de Pointes

i. Ventricular repolarization occurs during the QT interval, also referred to as the "refractory period"
ii. Increasing the time of the QT interval makes the ventricles "vulnerable" to arrhythmia, particularly Torsades de Pointes
iii. QTc = QT interval corrected for the heart rate
    1. Normal QTc in males ≈ 450 msec
    2. Normal QTc in females ≈ 440 msec
    3. Prolonged QTc interval > 500 msec

c. Additional risk factors for prolonged QT interval and/or Torsades de Pointes (Table 19)

Table 19. Risk Factors for Prolonged QT interval and Torsades de Pointes[30,31]

Patient-Specific Factors	Medication-Specific Factors
Female gender Hypokalemia Hypomagnesemia Bradycardia Recent conversion of arrhythmia Heart failure Baseline QT prolongation	Rapid administration Rapid dose titration Elevated drug concentration Drug-drug interactions Concomitant use of ≥ 2 medications that prolong QT interval

d. Medications associated with prolonged QTc interval[30--32] (Table 20)
    i. Defined by incidence
        1. Known risk –risk of QT prolongation and Torsades de Pointes supported by substantial evidence
        2. Possible risk –risk of QT prolongation documented but insufficient evidence for risk of Torsades de Pointes
        3. Conditional risk – risk of QT prolongation and Torsades de Pointes but only under certain conditions (i.e., overdose, electrolyte abnormalities, drug-drug interactions)

Table 20. Medications Associated with Prolonged QTc Interval and Torsades de Pointes[30-32]

Known Risk*	Possible Risk*	Conditional Risk*
Azithromycin	Aripiprazole	Amitriptyline
Class I Antiarrhythmic Drugs	Clozapine	Diphenhydramine
Class III Antiarrhythmic Drugs	Famotidine	Fluoxetine
Ciprofloxacin	Mirtazapine	Furosemide
Clarithromycin	Notriptyline	Hydroxychloroquine
Erythromycin	Olanzapine	Ketoconazole
Moxifloxacin	Risperidone	Metronidazole
Haloperidol	Tizanidine	Paroxetine
Methadone	Tolterodine	Quetiapine
Ondansetron	Venlafaxine	Trazodone
Thioridazine		Ziprasidone

*Lists are not all-inclusive; for complete list, refer to http://crediblemeds.org [formerly http://www.torsades.org].

Advanced Cardiac Life Support

I. Advanced Cardiac Life Support[8,33]

a. Basic tenants of cardiopulmonary resuscitation

i. Early defibrillation and high quality cardiopulmonary resuscitation (CPR) are key to successful resuscitation

ii. Interruptions in CPR should be minimized and as short as possible

iii. General treatment goals:

1. Restore spontaneous circulation (in the case of cardiac arrest)
2. Treat acute symptoms
3. Identify and treat underlying cause(s) and contributing factors – Table 21
4. Secondary prevention

Table 21. Differential Diagnosis for Reversible Causes of Cardiac Arrest ("The H's and T's")[8]

The "H's"	The "T's"
*H*ydrogen ion (acidosis)	*T*amponade (cardiac)
*H*ypo-/*H*yperkalemia	*T*ension pneumothorax
*H*ypothermia	*T*hrombosis, coronary
*H*ypoxia	*T*hrombosis, pulmonary
*H*ypovolemia	*T*oxins

b. General approach to the patient in cardiac arrest

i. Summon additional help

ii. Begin CPR

iii. Attach monitor/defibrillator

iv. Establish intravenous (IV) or intraosseous (IO) access

c. Medication considerations

i. Atropine: routine use during PEA or asystole no longer recommended as unlikely to be of benefit

ii. Sodium bicarbonate: routine use not recommended in cardiac arrest as not likely to be of benefit and risk for harm; should be reserved for specially selected situations (e.g, tricyclic antidepressant poisoning)

iii. Calcium: routine use in cardiac arrest not recommended as no beneficial effect demonstrated

d. Medication administration

i. IO route now routinely recommended in the setting of resuscitation

ii. All medications can be administered via IO route; IO dose = IV dose for resuscitation medications

iii. Medications should be administered at the beginning of the CPR cycle to maximize drug distribution

iv. As a last resort, medications can be administered via the endotracheal tube (ETT); however, IO administration is preferred and ETT administration should only be considered as a last resort when IV/IO access cannot be established
    1. Does not apply to all medications; medications that can be given via ETT:
        a. Lidocaine
        b. Epinephrine
        c. Atropine
        d. Naloxone
    2. ETT dose = 2.5 x IV dose (e.g., epinephrine 1 mg IV = 2.5 mg ETT)

e. Role of the pharmacist
    i. Medication procurement and preparation
    ii. Differential diagnosis
    iii. Medication information
    iv. Medication administration recommendations – e.g., alternate routes and dosages of medications

f. Post-resuscitation care is key aspect of for outcomes of associated with cardiac arrest[33]
    i. Therapeutic hypothermia in comatose patients
    ii. Electroencephalography (EEG) should be performed in comatose patients to evaluate for seizure activity
    iii. Aggressive resuscitation of hypotension
    iv. Advanced airway management
    v. Reversal/management of cause of arrest

II. Pulseless Cardiac Arrest[8]
    a. Ventricular fibrillation and pulseless ventricular tachycardia
        i. Treatment follows algorithm approach
        ii. Defibrillation with biphasic defibrillator at recommended starting dose per manufacturer (use 200 Joules if dose unknown) followed by immediate CPR; repeat every 2 minutes if arrhythmia persists
        iii. Medication therapy
            1. Epinephrine 1 mg IV/IO every 3—5 minutes
            2. Vasopressin no longer recommended – no benefit from epinephrine/vasopressin combination therapy
            3. Amiodarone 300 mg IV/IO bolus; may repeat with 150 mg if needed
                a. Can be considered if unresponsive to defibrillation and epinephrine
                b. Antiarrhythmic drug of choice due to increased survival to hospital admission
                c. Lidocaine may be considered as alternative if amiodarone not available or if administration via ETT needed; dose 1—1.5 mg/kg

IV/IO; may repeat with 0.5—0.75 mg/kg IV/IO if needed to maximum 3 mg/kg

4. Magnesium 1—2 g IV over 15 minutes should be given for polymorphic ventricular tachycardia with prolonged QTc interval (i.e., Torsades de Pointes)
5. Beta-blockers may be considered post-arrest; must assess benefit vs. risk (e.g., worsening hemodynamic instability, exacerbation of heart failure, etc.)

iv. Search, identify, and treat reversible causes (Table 21)

b. Pulseless electrical activity (PEA)
   i. Presence of electrical activity on ECG, but no corresponding mechanical activity (i.e., no pulse)
   ii. Treatment follows algorithm approach
   iii. Medication therapy
      1. Epinephrine 1 mg intravenous (IV)/Intraosseous (IO) every 3-5 minutes
      2. Note: atropine and vasopressin no longer recommended
   iv. Search, identify, and treat reversible causes (Table 21)

c. Asystole
   i. "Cardiac standstill:" complete lack of electrical or mechanical activity
   ii. Treatment follows algorithm approach
   iii. Medication therapy
      1. Epinephrine 1 mg intravenous (IV)/Intraosseous (IO) every 3—5 minutes
      2. Note: atropine and vasopressin no longer recommended
   iv. Search, identify, and treat reversible causes (Table 21)
   v. Consideration for termination of resuscitation efforts should be given in setting of prolonged asystole

Key Patient Counseling Points for Cardiac Arrhythmias

1. When prescribed an antiarrhythmic drug that requires multiple daily doses (e.g., BID or TID), the dose of each medication should be divided evenly based on time. For example, patients prescribed sotalol 80 mg BID should be instructed to take each dose 12 hours apart, as opposed to "at breakfast and dinner." Evenly spaced dosing intervals are critical to maximizing effective peak/trough concentrations while minimizing adverse events.
2. Patients prescribed an antiarrhythmic drug should be advised to inform all healthcare providers of the name and dose of the antiarrhythmic drug that they are prescribed, particularly when establishing services as a new patient. Additionally, patients should be advised to speak with their pharmacist prior to starting any new medication, including over-the-counter medications and supplements. These instructions are based upon both the rate and risk of drug-drug interactions associated with the antiarrhythmic drugs.
3. Patients should be advised on the potential adverse reactions that are associated with the individual antiarrhythmic drug that they are prescribed. Patients should be advised to contact their provider if they experience adverse reactions, particularly those that are either bothersome or that have potentially serious adverse outcomes, and that they should not stop taking the medication until they have contacted their provider and have been properly advised to do so.
4. Patients with atrial fibrillation that are prescribed long-term anticoagulation therapy should be counseled to monitor for potential adverse bleeding events, including extensive bruising or bruising without obvious injury, bleeding of the gums, nose bleeds, blood in the urine, dark colored stools, etc. Most importantly, patients should be advised to contact their provider as soon as they suspect abnormal and/or excessive bleeding.
5. Patients with atrial fibrillation that are prescribed long-term anticoagulation therapy should be advised to inform all healthcare providers of the name of dose of the medication that they are prescribed, particularly when establishing services as a new patient. Additionally, patients should be advised to speak with their pharmacist prior to starting any new medication, including over-the-counter medications and supplements. These instructions are based upon the risk for drug interactions with the anticoagulants, which can result in either an increase in the anticoagulant effect, potentially resulting in significant bleeding, or by decreasing the anticoagulant effect, thereby increasing the risk for stroke.

Guide to Abbreviations

Abbreviation	Term
ANA	Antinuclear antibody
AV	Atrioventricular [node]
bpm	Beats per minute
Ca	Calcium
CBC	Complete blood count
CYP	Cytochrome P450
ECG	Electrocardiogram
EEG	Electroencephalography
ER	Extended release
hr	Hour
ICDs	Implantable cardiac defibrillator
K	Potassium
LFTs	Liver function tests
min	Minute
Na	Sodium
PVCs	Premature ventricular contractions
SA	Sinoatrial [node]
SR	Sustained release
SVT	Supraventricular tachycardia
TSH	Thyroid stimulating hormone

Cardiac Arrhythmias & Advanced Cardiac Life Support

Core Therapeutic Module Series

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Disclosure

- I have nothing to disclose related to the content of this presentation

Learning Objectives

- Interpret signs, symptoms and diagnostic tests for cardiac arrhythmias.
- Identify drug-related problems, including drug interactions and adverse effects, associated with pharmacotherapy of cardiac arrhythmias.
- Identify and prevent drug-induced cardiac arrhythmias.
- Determine the most appropriate therapy and monitoring for cardiac arrhythmias based on patient-specific information and the most current guidelines.
- Utilize advanced cardiac life support (ACLS) guided therapies.

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 1

Rate Control versus Rhythm Control in Atrial Fibrillation

Patient Case Study 1 – History of Present Illness

CR is a 78 year-old male patient who was admitted to the hospital for intermittent shortness of breath and palpitations which have been present for approximately 1 week.

An initial electrocardiogram (ECG) obtained in the emergency department reveals atrial fibrillation.

Patient Case Study 1 – Assessment

Initial assessment reveals the following:

Assessment Variable	Recorded Measurement
Blood Pressure	158/94 mmHg
Heart Rate	78—88 bpm
Respiratory Rate	20 bpm
Physical Examination	Irregularly irregular rhythm; lungs clear to auscultation; otherwise WNL
Electrocardiogram (ECG)	Atrial fibrillation, rate 80—86 bpm

WNL = within normal limits

Patient Case Study 1 – Past Medical History

- The patient's past medical history is significant for:
  - Coronary artery disease
  - Myocardial infarction, 2009
  - Hyperlipidemia
  - Hypertension
  - Paroxysmal atrial fibrillation

Patient Case Study 1 – Medication History

- The patient's home medication regimen consists of:
  - Lisinopril 10 mg daily
  - Simvastatin 10 mg daily
  - Clopidogrel 75 mg daily
  - Aspirin 81 mg daily

Question 1 – Patient Case Study 1

Which of the following treatment recommendations for management of atrial fibrillation would be most appropriate at this time?

A. Attempt direct current cardioversion
B. Begin metoprolol succinate 50 mg po daily
C. Begin diltiazem extended-release 180 mg po daily
D. Begin amiodarone 200 mg po daily

Clinical Presentation of Atrial Fibrillation

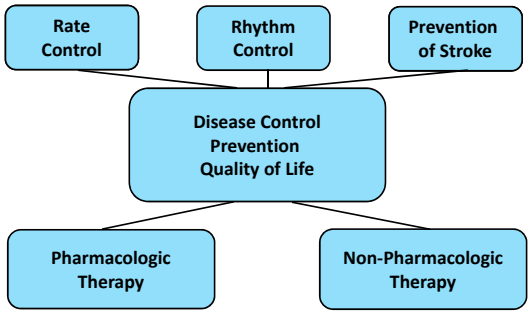
- Initial presentation varies greatly, from asymptomatic to unresponsive
  - Up to 90% of patients with paroxysmal atrial fibrillation have no awareness
- Presentation dependent upon several factors:
  - Duration of atrial fibrillation
  - Ventricular response (slow, fast, or normal)
  - Functional status of patient
  - Resultant hemodynamic and thromboembolic variables

Page RL et al. *Circulation.* 1994; 89:224-7
Israel CL et al. *J Am Coll Cardiol.* 2004 ;43:47-52
January CT et al. *Circulation.* 2014; 130:e199-267

Clinical Presentation of Atrial Fibrillation

Objective	Subjective
Irregularly irregular rhythm	Shortness of breath
Tachypnea	Fatigue
Variable heart rate	Weakness
Altered mental status	Palpitations
Hemodynamic instability	Dizziness
Heart failure	Syncope, presyncope
Stroke	Confusion

Treatment Considerations in Atrial Fibrillation



Treatment Considerations in Atrial Fibrillation

- Consideration should be given to patient-specific factors, such as:
  - Type and duration of atrial fibrillation
  - Severity and type of symptoms
  - Patient age
  - Co-morbid disease states
  - Treatment goals
  - Therapeutic options
- Must weigh *individual* risk and benefits

January CT et al. *Circulation.* 2014; 130:e199-267.

Atrial Fibrillation: Rate vs. Rhythm Control

- Rate control: focus on controlling ventricular rate with no regard to rhythm
- Rhythm control: attempt to restore and maintain sinus rhythm
- Both strategies, rate and rhythm control, are acceptable treatment options

Atrial Fibrillation: Rate vs. Rhythm Control

- *V*ery *I*mportant *P*aper: AFFIRM Trial
- Comparison of rate control to rhythm control in patients with atrial fibrillation
- Overall, no mortality benefit with rhythm control
  - Rate of stroke was similar
  - Rate of hospitalization higher in rhythm control

Wyse DG et al. *New Engl J Med.* 2002; 347:1825-33.

Clinical Decision Making: Rate vs. Rhythm Control

Favors Rate Control	Favors Rhythm Control
• Persistent AF • Permanent AF • Asymptomatic/few symptoms • Age > 65 years • Hypertension • Failure of AAD • Patient preference	• Initial episode of AF • Symptomatic AF • Frequent hospitalization • Failure on rate control • Age <65 years • No hypertension • Patient preference

AF = atrial fibrillation; AAD = antiarrhythmic drug

Connolly SJ et al. *Can J Cardiol.* 2005; 21 (Suppl B).
January CT et al. *Circulation.* 2014; 130:e199-267.

Question 1 – Revisited Patient Case Study 1

Which of the following treatment recommendations for management of atrial fibrillation would be most appropriate at this time?

A. Attempt direct current cardioversion
B. Begin metoprolol succinate 50 mg po daily
C. Begin diltiazem extended-release 180 mg po daily
D. Begin amiodarone 200 mg po daily

Patient Case Study 1 – Treatment Recommendation

Patient Assessment	Treatment Options
• Patient age: 78 years • Past Medical History: 1. Coronary artery disease 2. Myocardial infarction 3. Hyperlipidemia 4. Hypertension 5. Paroxysmal AF • Current medication regimen: 1. Lisinopril 10 mg daily 2. Simvastatin 10 mg daily 3. Clopidogrel 75 mg daily 4. Aspirin 81 mg daily	• Attempt direct current cardioversion • Begin metoprolol • Begin diltiazem • Begin amiodarone

Patient Case Study 1 – Monitoring Parameters

Safety	Efficacy
• Blood pressure • Heart rate • Electrocardiogram • Adverse reactions/events	• Symptom control – Palpitations – Shortness of breath – Dizziness – Weakness • Heart rate – Target < 80 bpm • Hospitalization

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 2

Stroke Prevention and Anticoagulation in Atrial Fibrillation

Patient Case Study 2 – History of Present Illness

BW is a 78 year-old female who was admitted to the hospital for a stroke.

During this hospitalization, the patient was diagnosed with non-valvular atrial fibrillation.

Patient Case Study 2 - Assessment

Other than residual effects of the stroke, the patient has had no symptom complaints related to the atrial fibrillation. Specifically, the patient denies palpitations and shortness of breath.

A review of the patient's medical record reveals that her blood pressure, heart rate, and electrocardiogram (ECG) have been consistent.

Patient Case Study 2 - Assessment

Assessment Variable	Recorded Measurement
Blood pressure	146/94 mmHg
Heart rate	88 bpm (irregular)
Respiratory Rate	18 bpm
Temperature	97.8° F
Electrocardiogram	Atrial fibrillation

Patient Case 2 - Past Medical History

- The patient's past medical history is significant for:
  - CVA
  - Atrial fibrillation
  - Hypertension
  - Urinary incontinence
  - Chronic kidney disease, stage 4 (creatinine clearance ≈ 18 mL/min)

Patient Case 2 - Medication History

- The patient's medication administration record (MAR) reveals:
  - Aspirin 325 mg every morning
  - Oxybutynin XR 15 mg daily
  - Metoprolol succinate 50 mg daily

Patient Case Study 2 - Assessment

You have been asked to speak with the patient regarding anticoagulation options for stroke prevention in atrial fibrillation.

The patient states that she has only been on aspirin and if at all possible, she would like to take a once daily medication.

Question 2 – Patient Case Study 2

What is the most appropriate treatment strategy for stroke prevention in this patient with atrial fibrillation?

A. Continue aspirin 325 mg daily
B. Begin warfarin 5 mg daily
C. Begin dabigatran 150 mg twice daily
D. Begin rivaroxaban 20 mg daily

Stroke Prevention in Atrial Fibrillation

- Atrial fibrillation is an independent risk factor for stroke, increasing risk ≈ 5 fold
  - Risk of ischemic stroke ≈ 5-6% *per year*
  - Diagnosed/undiagnosed strokes + transient ischemic attacks ≈ > 7% *per year*
- Risk for stroke remains in patients with:
  - Asymptomatic atrial fibrillation
  - Paroxysmal atrial fibrillation

Wolf PA et al. *Stroke*. 1991; 22:983-8.
Mozaffarian D et al. *Circulation*. 2015; 131:e29-322.
You JJ et al. *Chest*. 2012; 141:e531S-e575S.

Pathophysiology of Stroke in Atrial Fibrillation

- Blood stagnation in the left atrium and left atrial appendage as a result of ineffective contraction leads to thrombus formation
- Atrial fibrillation is associated with an increase in several prothrombotic markers → hypercoagulable
- Numerous structural changes occur in the atria, resulting in endothelial and endocardial damage

Watson T et al. *Lancet*. 2009; 373:155-66.

Risk Stratification – CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Criteria	Risk Score
Congestive heart failure	1 point
Hypertension	1 point
Age 75 years or greater	2 point
Diabetes mellitus	1 point
Stroke, TIA, or thromboembolism	2 points
Vascular disease	1 point
Age 65—74 years	1 point
Sex category (female gender)	1 point

January CT et al. *Circulation*. 2014; 130:e199-267.

CHA_2DS_2-VASc Score and Predicted Stroke Risk

CHA_2DS_2-VASc Score	Stroke Rate, % per year
1	1.3
2	2.2
4	4.0
6	9.8
9	15.2

January CT et al. *Circulation.* 2014; 130:e199-267.

Patient Case Study 2 – CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Criteria	Risk Score
*H*ypertension	1 point
*A*ge 75 years or greater	2 point
*S*troke, TIA, or thromboembolism	2 points
*S*ex *c*ategory (female gender)	1 point

Stroke Prevention Recommendations

CHA_2DS_2-VASc Score	Recommendation
0	No therapy recommended
1	Oral anticoagulation, aspirin, or no therapy
2+	Oral anticoagulation
Any score with prior stroke or TIA	Oral anticoagulation

January CT et al. *Circulation.* 2014; 130:e199-267.

Stroke Prevention in Atrial Fibrillation

- When oral anticoagulation is recommended, may use:
  - Warfarin
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban

January CT et al. *Circulation.* 2014; 130:e199-267.

Anticoagulants in Atrial Fibrillation: Efficacy

Drug	Efficacy vs. Warfarin
Dabigatran	Superior for ischemic stroke prevention
Rivaroxaban	Non-inferior for ischemic stroke prevention
Apixaban	Superior for ischemic and hemorrhagic stroke prevention
Edoxaban	Non-inferior for ischemic stroke prevention

Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51. Patel MR et al. *N Engl J Med.* 2011; 365:883-91
Granger CB et al. *N Engl J Med.* 2011; 365:981-92. Guigliano RP et al. *N Engl J Med.* 2013; 369:2093-104

Anticoagulants in Atrial Fibrillation: Safety Comparison

Drug	Rate of Bleeding vs. Warfarin*
Dabigatran	Lower rate of bleeding, increased gastrointestinal bleeding
Rivaroxaban	Similar rate of bleeding, increased gastrointestinal bleeding and transfusion
Apixaban	Lower rate of bleeding
Edoxaban	Lower rate of bleeding, increased gastrointestinal bleeding

*Bleeding includes both major and minor bleeding, including intracranial hemorrhage

Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51. Patel MR et al. *N Engl J Med.* 2011; 365:883-91
Granger CB et al. *N Engl J Med.* 2011; 365:981-92. Guigliano RP et al. *N Engl J Med.* 2013; 369:2093-104

Anticoagulation in Atrial Fibrillation

- Selection of an anticoagulation based on patient-specific factors
- Patient-specific factors to consider:
  - Co-morbid conditions
  - Patient preference
  - Previous experience on anticoagulants
  - Drug interactions
  - Cost

Anticoagulation in Atrial Fibrillation: Impact of Co-morbidities

Disease State	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanical valve	✓				
Obesity	✓				
Peripheral artery disease	✓				
Liver disease	✓	✓			
Renal disease		✓	✓	✓	✓
Hemodialysis	✓			✓	

Pradaxa® [package insert]. Xarelto® [package insert]. Eliquis® [package insert].Savaysa® [package insert].

Anticoagulation in Atrial Fibrillation: Dose Adjustments

Medication	Recommended Dose Adjustment
Dabigatran	Typical dose: 150 mg twice daily CrCl 30—50 mL/min + DI: 75 mg twice daily* CrCl 15—30 mL/min: 75 mg twice daily CrCl <15 mL/min or dialysis: avoid
Rivaroxaban	Typical dose: 20 mg once daily CrCl 15—50 mL/min: 15 mg once daily CrCl <15 mL/min: avoid

CrCl = creatinine clearance
*DI: drug interaction with ketoconazole or dronedarone

Pradaxa® [package insert]. Xarelto® [package insert].

Anticoagulation in Atrial Fibrillation: Dose Adjustments

Medication	Recommended Dose Adjustment
Apixaban	Typical dose: 5 mg twice daily Adjust to 2.5 mg daily if 2 of following: ≥ 80 years, body weight ≤ 60 kg, SCr ≥1.5 mg/dL Hemodialysis: 2.5 mg twice daily
Edoxaban	Typical dose: 60 mg once daily CrCl > 95 mL/min: avoid CrCl 15—50 mL/min: 30 mg once daily CrCl < 15 mL/min: avoid

CrCl = creatinine clearance

Eliquis® [package insert]. Savaysa™ [package insert].

Question 2 – Revisited
Patient Case Study 2

What is the most appropriate treatment strategy for stroke prevention in this patient with atrial fibrillation?

A. Continue aspirin 325 mg daily
B. Begin warfarin 5 mg daily
C. Begin dabigatran 150 mg twice daily
D. Begin rivaroxaban 20 mg daily

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 3

Treatment Considerations for Atrial Fibrillation with a Rapid Ventricular Response

Patient Case Study 3 – History of Present Illness

During bedside rounds, you enter the room of patient BW, a 67 year-old patient who is currently admitted to the hospital for treatment of pneumonia.

Upon entering the room, the team observes that the patient is breathing rapidly, diaphoretic, and appears in acute distress.

Patient Case Study 3 – Assessment

Upon questioning, the patient reports increased shortness of breath and chest pain, which began approximately 30 minutes ago.

A rapid assessment reveals the following:

Assessment Variable	Recorded Measurement
Blood pressure	136/76 mmHg
Heart rate	148 bpm
Respiratory rate	28 bpm

Patient Case Study 3 – Assessment

Bedside telemetry reveals atrial fibrillation with a ventricular rate of 148-160 bpm.

The patient's past medical history is significant for chronic obstructive pulmonary disease (COPD) and hypertension.

The patient has no history of atrial fibrillation.

Question 3 – Patient Case Study 3

Which of the following is the most appropriate treatment recommendation for the patient at this time?

A. Attempt direct current cardioversion
B. Administer metoprolol tartrate 50 mg PO x one dose
C. Administer digoxin 0.25 mg IV x one dose
D. Administer diltiazem 15 mg IV x one dose

Atrial Fibrillation with Rapid Ventricular Response

- The ventricular response to atrial fibrillation is dependent on the AV node to act as a "filter"
- Inadequacy of the filter can result in a rapid ventricular response (RVR)
- RVR is associated with a decrease in cardiac output and potential for hemodynamic instability

Clinical Presentation of Atrial Fibrillation with Rapid Ventricular Response

Objective	Subjective
Altered mental status	Angina
Syncope	Chest "pressure"
Tachycardia	Dyspnea/shortness of breath
Hemodynamic instability	Fatigue
Ischemic ECG changes	Palpitations
Cardiomyopathy	Mental status changes
Heart failure (acute)	Loss of consciousness

Treatment Goals for Rapid Ventricular Response

- Focus 1: prevent hemodynamic instability and further clinical deterioration associated with uncontrolled rate
- Focus 2: improve symptoms
- Focus 3: avoid cardiac remodeling associated with tachycardia

Treatment Considerations for Rapid Ventricular Response

Symptomatic?	Hemodynamically Stable?	Initial Treatment Recommendation
No	Yes	AV-node blocking agents; oral route
Yes	Yes	AV-node blocking agents; intravenous route
Yes	No	Direct current cardioversion

January CT et al. *Circulation.* 2014; 130:e199-267.

Intravenous Treatment Options for Rapid Ventricular Rate Control

Medication	Initial Dose	Repeat Dose(s)	Considerations
Amiodarone	150 mg IV	0.5—1 mg/min	Preferred in patients with acute heart failure
Diltiazem	0.25 mg/kg IV	5—15 mg/hour	↓ BP; Caution in HF
Verapamil	0.075—0.15 mg/kg IV	NA	↓ BP; Caution in HF
Esmolol	500 mcg/kg IV	50—200 mcg/kg/min	↓ BP; Caution in HF, asthma
Metoprolol	2.5—5 mg IV	May repeat to total of 3 doses (15 mg)	↓ BP; Caution in HF, asthma

HF = heart failure; IV = intravenous; NA = not applicable; BP = blood pressure

January CT et al. *Circulation.* 2014; 130:e199-267.

Question 3 – Revisited Patient Case Study 3

Which of the following is the most appropriate treatment recommendation for the patient at this time?

A. Attempt direct current cardioversion
B. Administer metoprolol tartrate 50 mg PO x one dose
C. Administer digoxin 0.25 mg IV x one dose
D. Administer diltiazem 15 mg IV x one dose

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 4

Antiarrhythmic Drug Interactions

Patient Case Study 4 – History of Present Illness

KD is a 68 year-old male patient who presents to the ambulatory care clinic for his annual physical examination.

The physician indicates that the patient will require at least a 30% reduction in his LDL-cholesterol and that she would like to start the patient on a statin.

Patient Case Study 4 – Medication History

- The patient's medication regimen consists of:
  - Amiodarone 400 mg daily
  - Aspirin 81 mg daily
  - Metoprolol succinate 50 mg daily
  - Metformin 500 mg twice daily
- The patient's insurance formulary includes simvastatin and atorvastatin on the preferred list.

Question 4 – Patient Case Study 4

Which of the following is the most appropriate treatment recommendation for this patient?

A. Start simvastatin 20 mg daily
B. Start simvastatin 40 mg daily
C. Start atorvastatin 10 mg daily
D. Start atorvastatin 80 mg daily

Drug Interactions of the Antiarrhythmic Drugs

- Antiarrhythmic drugs associated with extensive and significant interactions
  - Especially with other cardiac medications
  - May result in clinically significant outcomes
- Primarily a result of cytochrome (CYP) P450 isoenzymes

Cytochrome (CYP) P450 Activity of the Antiarrhythmic Drugs

CYP Enzyme	Substrate	Inhibitor
CYP 1A2	Lidocaine Mexiletine Propafenone	Lidocaine Mexiletine
CYP 2C9	—	Amiodarone
CYP 2D6	Flecainide Mexiletine Propafenone Dronedarone	Amiodarone Dronedarone Flecainide Propafenone Quinidine
CYP 3A4	Amiodarone Dronedarone Disopyramide Lidocaine Propafenone Quinidine	Quinidine Amiodarone Dronedarone

Micromedex® 2.0 Healthcare Series.
Anderson JR et al. *Cardiol Clin.* 2001; 19:215-34.

Mechanism of Antiarrhythmic Drug Interactions

- In addition, antiarrhythmic drug interactions can occur as a result of:
  - P-glycoprotein (quinidine)
  - Renal cation transport system (dofetilide)
  - Pharmacodynamic interactions (e.g., additive beta-adrenergic blockade)

Examples of Antiarrhythmic-Cardiovascular Drug Interactions

Antiarrhythmic Drug	Other Cardiovascular Medications*
Amiodarone	Apixaban, Atorvastatin, Beta-Blockers, Calcium Channel Blockers, Clopidogrel, Dabigatran, Digoxin, Diltiazem, Fluvastatin, Irbesartan, Losartan, Rivaroxaban, Simvastatin, Torsemide, Verapamil, Warfarin
Dofetilide	Diuretics, Hydrochlorothiazide, Ranolazine, Triamterene, Vasopressin, Verapamil
Propafenone	Metoprolol, Ranolazine, Propanolol, Vasopressin, Warfarin
Quinidine	Aspirin, Atenolol, Diltiazem, Digoxin, Metoprolol, Nifedipine, Propranolol, Ranolazine, Vasopressin, Verapamil, Warfarin
Sotalol	Beta-Blockers, Clonidine, Digoxin, Diltiazem, Diuretics, Ranolazine, Vasopressin, Verapamil

*This chart is for illustrative purposes and is not meant to be all-inclusive

Micromedex® 2.0 Healthcare Series.
Anderson JR et al. *Cardiol Clin.* 2001; 19:215-34.

Considerations for Combination Use of Amiodarone and Statins

- US Food & Drug Administration (FDA) released statement restricting simvastatin dose when used in combination with amiodarone
  - Due to increased risk for rhabdomyolysis, kidney failure, and death
  - Maximum simvastatin dose = 20 mg daily
- Simvastatin and lovastatin appear to be most affected by amiodarone drug interaction; atorvastatin less affected

US FDA Communication, 8/8/2008
Bottorff MB et al. *Am J Cardiol.* 2006; 97[suppl]:27C-31C

Question 4 – Revisited Patient Case Study 4

Which of the following is the most appropriate treatment recommendation for this patient?

A. Start simvastatin 20 mg daily
B. Start simvastatin 40 mg daily
C. Start atorvastatin 10 mg daily
D. Start atorvastatin 80 mg daily

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 5

Adverse Events Associated with Antiarrhythmic Drugs: QTc Prolongation and Torsades de Pointes

Patient Case Study 5 – History of Present Illness

The resuscitation team had just successfully resuscitated a patient in room 307. The team reports that the initial rhythm displayed on the monitor was Torsades de Pointes.

You are asked to determine if any medications in the patient's current regimen could have contributed to the cardiac arrest.

Patient Case Study 5 – Assessment

- A post-arrest electrocardiogram (ECG) is available and reveals the following:
  - Impression: sinus tachycardia with global ST-segment depression
  - Heart Rate: 108 bpm
  - QTc Interval: 647 msec

Patient Case Study 5 – Medication History

Home Medication List	Hospital Medication List*
• Dofetilide 500 mg q 12 hours • Lisinopril 20 mg daily • Metoprolol 50 mg daily • Hydrochlorothiazide 25 mg daily • Amitriptyline 25 mg daily • Warfarin 5 mg daily	• Moxifloxacin 400mg IV daily • Methylprednisolone 80 mg IV every 12 hours • Albuterol by nebulizer every 6 hours as needed • Ipratropium by nebulizer every 6 hours as needed • Sodium chloride 0.9% @ 100 mL/hour

*All home medications were continued at admission

Question 5 – Patient Case Study 5

Which of the following medications *most likely* contributed to QTc prolongation resulting in Torsades de Pointes in this patient?

A. Amitriptyline, hydrochlorothiazide, and albuterol
B. Moxifloxacin, ipratropium, and warfarin
C. Amitriptyline, methylprednisolone, and metoprolol
D. Dofetilide, amitriptyline, and moxifloxacin

QTc Interval Prolongation

- Ventricular repolarization occurs during the QT interval, also referred to as the "refractory period"
- Increasing the time of the QT interval makes the ventricles "vulnerable" to arrhythmia, particularly Torsade de Pointes
- QTc = QT interval corrected for the heart rate
  - Normal QTc in males = 450 msec
  - Normal QTc in females = 440 msec

Roden DM. *N Engl J Med.* 2004; 350:1013-22
Drew BJ et al. *Circulation.* 2010; 121:1047-60

Risk Factors for Torsade de Pointes

Patient-Specific Factors	Medication-Related Factors
• Female gender • Hypokalemia • Hypomagnesemia • Bradycardia • Recent conversion of arrhythmia • Heart failure • Baseline QT prolongation	• Rapid administration • Rapid dose titration • Elevated medication concentration • Concomitant use of ≥ 2 medications that prolong QT interval • Drug-drug interactions

Roden DM. *N Engl J Med.* 2004; 350:1013-22
Drew BJ et al. *Circulation.* 2010; 121:1047-60

Medications Associated with QT Prolongation and Torsade de Pointes

Known Risk*	Possible Risk*	Conditional Risk*
• Azithromycin • Class I antiarrhythmics • Class III antiarrhythmics • Ciprofloxacin • Clarithromycin • Erythromycin • Haloperidol • Methadone • Moxifloxacin • Ondansetron • Thioridazine	• Aripiprazole • Clozapine • Famotidine • Mirtazipine • Nortriptyline • Olanzapine • Risperidone • Tizanidine • Tolterodine • Venlafaxine	• Amitriptyline • Fluoxetine • Furosemide • Ketoconazole • Metronidazole • Paroxetine • Quetiapine • Trazodone • Ziprasidone

*For a complete list, see: http://crediblemeds.org

Drew BJ et al. *Circulation.* 2010; 121:1047-60.

Dofetilide Drug Interactions

- Metabolized via CYP 3A4 (minor) and eliminated via renal cation transport system
- Drug interactions via CYP 3A4: *"...Inhibitors of this isoenzyme should be cautiously co-administered with [dofetilide]..."*
  - Examples: macrolide antibiotics, azole antifungals, protease inhibitors, serotonin reuptake inhibitors, amiodarone
- Concomitant use with other medications that prolong the QT interval is not recommended
  - Examples: phenothiazines, tricyclic antidepressants, macrolide antibiotics, fluoroquinolone antibiotics
  - Other Class I or Class III antiarrhythmic drugs – "wash out" period required

Tikosyn® [package insert]. Pfizer, Inc. 2014.

Dofetilide Drug Interactions

- Contraindicated in combination with renal cation transport inhibitors
  - Contraindicated: cimetidine, trimethoprim, ketoconazole, megestrol, and prochlorperazine
  - Extreme caution: amiloride, triamterene, and metformin
- In addition, use extreme caution with:
  - Potassium- and magnesium-wasting diuretics (e.g., furosemide)
  - "Other cardiovascular drugs"

Tikosyn® [package insert]. Pfizer, Inc. 2014.

Question 5 – Revisited
Patient Case Study 5

Which of the following medications *most likely* contributed to QTc prolongation resulting in Torsades de Pointes in this patient?

A. Amitriptyline, hydrochlorothiazide, and albuterol
B. Moxifloxacin, ipratropium, and warfarin
C. Amitriptyline, methylprednisolone, and metoprolol
D. Dofetilide, amitriptyline, and moxifloxacin

Pharmacotherapy Considerations in Cardiac Arrhythmias & Advanced Cardiac Life Support:

Patient Case Study 6

Pharmacotherapy Considerations in Advanced Cardiac Life Support

Patient Case 6 – History of Present Illness

The resuscitation team is called to the bedside of a patient in cardiopulmonary arrest secondary to an acute myocardial infarction. The monitor displays ventricular fibrillation.

The patient has received defibrillation x 3 and epinephrine 1 mg x 2 but remains in ventricular fibrillation.

Question 6 – Patient Case Study 6

Which of the following treatment recommendations is most appropriate for this patient at this time?

A. Administer amiodarone 150 mg IV
B. Administer amiodarone 300 mg IV
C. Administer lidocaine 1.5 mg/kg IV
D. Administer magnesium sulfate 2 g IV

Antiarrhythmic Drugs in Cardiac Arrest

- Antiarrhythmic drugs may be utilized in the following resuscitation settings:
  - Ventricular fibrillation
  - Ventricular tachycardia
  - Supraventricular tachycardia
  - Atrial fibrillation with rapid ventricular response
  - Other tachyarrhythmias

Link MS et al. *Circulation* 2015; 132: S444-64.

Antiarrhythmic Drugs for Pulseless Cardiac Arrest

- Amiodarone is considered the first line antiarrhythmic drug for pulseless cardiac arrest
- Amiodarone demonstrated improved rate of survival to hospital admission when compared to lidocaine in out-of-hospital arrest
- Amiodarone dose
  - Pulseless cardiac arrest = 300 mg
  - Arrhythmia with pulse = 150 mg

Kudenchuk PJ et al. *New Engl J Med.* 1999; 341:871-8
Dorian P et al. *New Engl J Med.* 2002; 346:884-90
Link MS et al. *Circulation* 2015; 132: S444-64

Antiarrhythmic Drugs for Pulseless Cardiac Arrest

- Lidocaine may be considered an alternative only when "*amiodarone is unavailable*" or ETT administration needed
  - First dose = 1—1.5 mg/kg IV
  - May repeat 0.5—0.75 mg/kg IV, to maximum of 3 mg/kg IV
- Magnesium may be considered in Torsades de Pointes associated with a prolonged QT interval

Link MS et al. *Circulation* 2015; 132: S444-64.

Question 6 – Revisited
Patient Case Study 6

Which of the following treatment recommendations is most appropriate for this patient at this time?

A. Administer amiodarone 150 mg IV
B. Administer amiodarone 300 mg IV
C. Administer lidocaine 1.5 mg/kg IV
D. Administer magnesium sulfate 2 g IV

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    - Note that guidelines have subsequently changed since the publication of this article, but still an excellent resource in terms of scope and depth of information covered.

QUESTIONS IN PRESENTATION

Patient Case 1: CR is a 78 y/o male patient who was admitted to the hospital for intermittent shortness of breath and palpitations which has been present for approximately 1 week. An initial electrocardiogram (ECG) obtained in the emergency department reveals atrial fibrillation. Initial assessment reveals BP 158/94 mmHg, HR 78-88 bpm, RR 20 bpm. Physical exam irregularly irregular rhythm, lungs clear to auscultation, otherwise normal. ECG: atrial fibrillation, rate 80-86 bpm. PMH significant for: coronary artery disease, myocardial infarction (2009), hyperlipidemia, hypertension, paroxysmal atrial fibrillation. Home medication regimen: lisinopril 10mg daily, simvastatin 10 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily.

1. Which of the following treatment recommendations for management of atrial fibrillation would be most appropriate at this time?
    a. Attempt direct current cardioversion
    b. Begin metoprolol succinate 50 mg po daily
    c. Begin diltiazem extended-release 180 mg po daily
    d. Begin amiodarone 200 mg daily

Patient Case 2: BW is a 78 year-old female who was recently admitted to after the hospital for a stroke. During the hospitalization, the patient was diagnosed with atrial fibrillation. Other than residual effects of the stroke, the patient has had no symptom complaints related to the atrial fibrillation. Specifically, the patient denies palpitations and shortness of breath. A review of the patient's medical record reveals that her BP, HR and ECG have been consistent. Current vitals: BP 146/94 mm Hg, HR 88 bpm (regular), RR 18 bpm, temperature 97.8°F, ECG atrial fibrillation. Past Medical History: CVA, Atrial Fibrillation, Hypertension, Urinary Incontinence, CKD Stage 4 (ClCr 18 ml/min). The patient's medication administration record reveals: aspirin 325 mg every morning, oxybytynin XR 15 mg daily, metoprolol succinate 50 mg daily. You have been asked to speak with the patient regarding anticoagulation options for stroke prevention in atrial fibrillation. The patient states that she has only been on aspirin and if at all possible, she would like to take a once daily medication.

2. What is the most appropriate treatment strategy for stroke prevention in this patient with atrial fibrillation?
    a. Continue aspirin 325 mg dialy
    b. Begin warfarin 5 mg daily
    c. Begin dabigatran 150 mg twice daily
    d. Begin rivaroxaban 20 mg daily

Patient Case 3: During bedside rounds, you enter the room of patient BW, a 67 year-old patient who is currently admitted to the hospital for treatment of pneumonia. Upon entering the room, the team observes that the patient is breathing rapidly, diaphoretic and appears in acute distress. Upon questioning, the patient reports increased shortness of breath and chest pain, which began approximately 30 minutes ago. A rapid assessment reveals the following: BP 136/76 mmgHg, HR 148 bpm, RR 28 bpm. Bedside telemetry reveals atrial fibrillation with ventricular rate of 148-160bpm. The patient's past medical history is significant for COPD and hypertension. The patient has no history of atrial fibrillation.

3. Which of the following is the most appropriate treatment recommendation for the patient at this time?
    a. Attempt direct current cardioversion
    b. Administer metoprolol tartrate 50 mg PO x one dose
    c. Administer digoxin 0.25 mg IV x one dose
    d. Administer diltiazem 15 mg IV x one dose

Patient Case #4: KD is a 68 y/o male patient who presents to the ambulatory care clinic for his annual physical examination. The physician indicates that the patient will require at least a 30% reduction in his LDL-cholesterol, and that she would like to start the patient on a statin. The patient's medication regimen consists of: amiodarone 400 mg daily, aspirin 81 mg daily, metoprolol succinate 50 mg daily, metformin 500 mg twice daily. The patient's insurance formulary includes simvastatin and atorvastatin on the preferred list.

4. Which of the following is the most appropriate treatment recommendation for this patient?
    a. Start simvastatin 20 mg daily
    b. Start simvastatin 40 mg daily
    c. Start atorvastatin 10 mg daily
    d. Start atorvastatin 80 mg daily

Patient Case #5: The resuscitation team had just successfully resuscitated a patient in room 307. The team reports that the initial rhythm displayed on the monitor was Torsade de Pointes. You are asked to determine if any medications in the patient's current regimen could have contributed to the cardiac arrest. A post-arrest electrocardiogram is available and reveals the following: sinus tachycardia with global ST-segment depression, HR 108 bpm, QTc interval 647 msec. Home medications (continued at admission): dofetilide 500mg Q12H, lisinopril 20 mg daily, metoprolol 50 mg daily, hydrochlorothiazide 25 mg daily, escitalopram 10 mg daily, warfarin 5 mg daily. Hospital medication list: moxifloxacin 400 mg IV daily, methylprednisolone 80 mg IV every 12 hours, albuterol by nebulizer every 6 hours as needed, ipratropium by nebulizer every 6 hours as needed, sodium chloride 0.9% @ 100 mL/hr.

5. Which of the following medications most likely contributed to QTc prolongation resulting in Torsade de Pointes in this patient?
    a. Amitriptyline, hydrochlorothiazide, and albuterol
    b. Moxifloxacin, ipratropium, and warfarin
    c. Amitriptyline, methylprednisolone, and metoprolol
    d. Dofetilide, amitriptyline, and moxifloxacin

Patient Case #6: The resuscitation team is called to the bedside of a patient in cardiopulmonary arrest secondary to an acute myocardial infarction. The monitor displays ventricular fibrillation. The patient has received defibrillation x 3 and epinephrine 1 mg x 2, but remains in ventricular fibrillation.

6. Which of the following treatment recommendations is most appropriate for this patient at this time?
    a. Administer amiodarone 150 mg IV
    b. Administer amiodarone 300 mg IV
    c. Administer lidocaine 1.5 mg/kg IV
    d. Administer magnesium sulfate 2 g IV

ANSWERS

1. B
2. B
3. D
4. C
5. D
6. B