RUTGERS
School of Health Related Professions

Cardiovascular Pharmacology 2015

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Learning Objectives

- Describe the indications, contraindications, interactions, and adverse effects of medications used in the treatment of:
  - Heart failure
  - Hypertension
  - Cardiac arrhythmias
- Review the categories of antilipemic medications, including the advantages and disadvantages, contraindications, and adverse effects

Congestive Heart Failure (CHF)

- Progressive syndrome where **the heart can not fill with or eject blood adequately** to meet the demands of the body
- **Systolic heart failure**
  - E.g., heart failure with reduced ejection fraction
  - The heart can not eject enough blood from the ventricles because of **thin weak muscles**
- **Diastolic heart failure**
  - E.g., heart failure with preserved ejection fraction
  - Problem of filling the ventricles secondary to **high thickness of the ventricular wall** which does not leave enough empty space in the ventricular cavity for blood to pour into

Guidelines for management of heart failure. *Circulation*. 2013;128:e240-e327.

Heart Failure Stages

Stage	Definition	Examples
A	High risk of developing heart failure	HTN, atherosclerosis, DM, obesity, metabolic syndrome
B	Structural heart disease, but no signs or symptoms of heart failure	Prior MI, LVH, LV systolic dysfunction
C	Structural heart disease and current or previous signs and symptoms	LV systolic dysfunction with fatigue, dyspnea, reduced exercise tolerance
D	Refractory heart failure requiring specialized interventions	•Refractory signs and symptoms at rest despite maximal medical therapy •Recurrent hospitalizations •Living with mechanical assist device

Adaptive Mechanisms in HF

Compensatory Response	Benefits of Compensation	Detriments of Compensation
Increased preload	Optimize stroke volume	Congestion ↑ MVO_2
Vasoconstriction	Maintain BP	↑ MVO_2 ↑ Afterload/↓ SV
Tachycardia and ↑ contractility	Maintain cardiac output	↑ MVO_2 ↓ diastolic filling time
Ventricular hypertrophy	Maintain cardiac output	Diastolic/systolic dysfunction

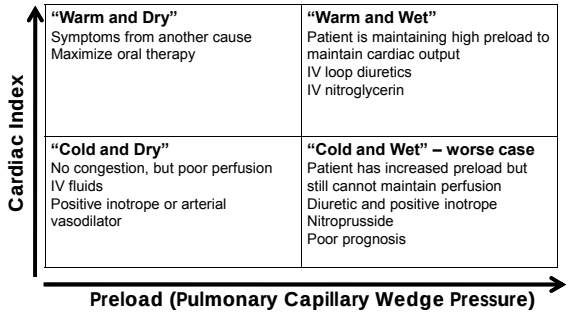
Systolic Heart Failure Medications

Reduce Mortality	Improve Symptoms
Angiotensin-converting enzyme (ACE) inhibitors	Digoxin
Angiotensin receptor blockers (ARBs)	Diuretics
β-blockers	
Aldosterone antagonists	
Nitrate + hydralazine combination	

Management of Diastolic Dysfunction

- Control blood pressure
- Maintain appropriate ventricular rate
- Diuretics as-needed
- β-blockers in patients with a prior history of:
  - Atrial fibrillation
  - Myocardial infarction
  - Hypertension

Acute Decompensated HF

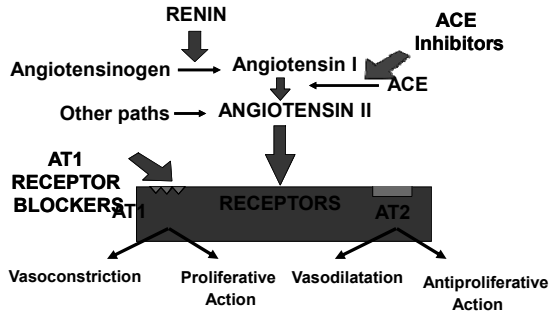


Guidelines for Management of heart failure. *Circulation*. 2013;128:e240-e327

Angiotensin Converting Enzyme (ACE) Inhibitors

- Cornerstones of heart failure management
  - Block conversion of angiotensin I → angiotensin II → decrease SVR and afterload
  - Increase bradykinin
  - Improve clinical symptoms and hemodynamic variables
  - Reduce mortality

Mechanism of Action



ACE Inhibitors

- **Indications**
  - All patients with a history of MI
    - Regardless of EF or presence of HF symptoms
  - Patients with a reduced EF and no symptoms of HF
    - Even if they have not experienced MI
- **Contraindications**
  - Hypersensitivity
  - Bilateral renal artery stenosis (RAS)
  - History of angioedema
  - Pregnancy

Adverse Effects

C – Cough
A – Angioedema
P – Potassium (increase)
T – Taste disturbance
O – Orthostatic hypotension
P – Pregnancy (contraindicated)
R – Renal failure (in bilateral RAS)
IL – Idiosyncratic Leukopenia

ACE Inhibitors Summary

Drug	Initial Dose	Maximum Dose
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Fosinopril	5-10 mg once daily	40 mg once daily
Lisinopril	2.5-5 mg once daily	20-40 mg once daily
Quinapril	10 mg twice daily	40 mg twice daily
Ramipril	1.25-2.5 mg once daily	10 mg once daily

Angiotensin Receptor Blockers (ARBs)

- **Mechanism of action**
  - Direct antagonism of the angiotensin II receptors
    - Displaced angiotensin II from the AT1 receptor
    - Preserve AT2 receptor activity
- **Indications**
  - Alternatives for ACE inhibitors
    - No cough, angioedema?

Beta Blockers in Heart Failure: Indications

- Beta-blockers and ACEIs should be used in all patients with a history of MI
  - **Regardless** of EF or presence of HF
- Beta-blockers are indicated in all patients without a history of MI who have a reduced left ventricular ejection fraction (LVEF)

Beta Blockers

- **Adverse effects**
  - Worsening HF and fluid retention
  - Fatigue
  - Bradycardia and heart block
  - Hypotension
- **Precautions**
  - Asthma, diabetes (with hypoglycemia), peripheral vascular disease
- **Relative contraindications**
  - Heart rate <60 bpm unless paced
  - SBP <100 mmHg
  - Moderate or severe left ventricular failure
  - Shock
  - PR-interval >0.24 seconds
  - 2nd or 3rd heart block

Beta Blockers Summary

Drug	Initial Dose	Maximum Dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily (50 mg for patients > 85 kg)
Carvedilol extended release	10 mg once daily	80 mg once daily
Metoprolol tartrate	6.25 mg twice daily	75 mg twice daily
Metoprolol succinate extended release	12.5-25 mg once daily	200 mg once daily

Aldosterone Antagonists

- **Agents**
  - Spironolactone and eplerenone
- **Mechanism of action**
  - Direct antagonism of aldosterone on sodium-potassium pump and mineralocorticoid receptors in late distal tubule
  - Cause increased sodium excretion and increased potassium retention
  - Prevents myocardial hypertrophy
  - Results in hyperkalemia

Aldosterone Antagonists and Adverse Effects

- **Gynecomastia**
  - Rarely occurs with epleronone
- **Hyperkalemia**
  - Avoid K supplements
  - Frequent monitoring of potassium
  - Patients with K > 5 mEq/L OR S_{Cr} > 2.5 mg/dL were excluded from the RALES study

Summary: Drugs that Improve Mortality in Heart Failure

Class	Adverse Events	Notes
ACE Inhibitors	Hyperkalemia, hypotension, cough, angioedema, renal dysfunction	Preferred over ARBs Pregnancy Category X Higher doses may be of more benefit All ACEIs are probably equivalent
Angiotensin II Receptor Blockers	Hyperkalemia, hypotension, renal dysfunction	No cough Not preferred unless patient ACEI intolerant All ARBs are probably equivalent
Aldosterone Antagonists	Hyperkalemia, renal dysfunction	Hormonal AEs with spironolactone Use low doses throughout treatment
β-blockers	Fluid retention, fatigue, bradycardia	Patients may see no symptomatic improvement Continue even if acutely decompensated
Nitrate/ hydralazine	HA, hypotension	No hospitalization reduction Esp. useful for African-Americans

Digoxin

- **Mechanism of action**
  - Inhibition of sodium/potassium ATPase pump
    - Increases the intracellular sodium-calcium exchange by blocking Na^+/K^+/ATPase in the cell membrane
  - Decreases the activity of the Na^+/Ca^{2+} exchanger
    - Increases intracellular Na^+
    - Results in increase intracellular Ca^{2+} concentrations
    - Increased intracellular calcium leads to increased contractility of the heart muscle
- **Dosing**
  - Initial dose: 0.125-0.25 mg once daily
  - Maximum dose: 0.125-0.25 mg once daily
    - Caution in renal impairment; adjust dosing interval accordingly

Digoxin: Adverse Effects

- ***Digitalis* toxicity**
  - Sinus bradycardia
  - AV block
  - Drowsiness
  - Fatigue
  - Vomiting, nausea
  - Visual hallucinations, blurred vision, halos, diplopia
- **Cardiac**
  - Dysrhythmias
  - Complete heart block
- **Gastrointestinal**
  - Anorexia, nausea, vomiting
- **Central nervous system**
  - Headache, fatigue, confusion

Therapeutic serum level = 0.5-2 ng/mL

Patient Selection for Digoxin

- **Only for <u>symptomatic patients</u>**
  - As adjunctive treatment to improve symptoms
  - For early symptom relief while awaiting benefits of ACEIs and Beta-blockers
  - For patients with concurrent AF and HF
    - Beta-blocker may control ventricular rate better
- **No effect on mortality!**

Diuretics

- **Loops**
  - Furosemide
  - Bumetanide
  - Torsemide
- **Thiazides**
  - Hydrochlorothiazide
  - Chlorthalidone
  - Chlorothiazide
  - Metolazone

Important Points Regarding Loop Diuretics in HF

- Effect on morbidity and mortality?
- Provide the quickest symptomatic relief
  - Hours vs. weeks to months for other drugs
- Should not be used alone
- Inappropriate dose can increase risk of:
  - Hypotension
  - Renal insufficiency with other agents

Loop Diuretics: Mechanism of Action

- Inhibit the $Na^+/K^+/2Cl^-$ cotransporter in the ascending limb of the loop of Henle
  - Results in decreased absorption of sodium and chloride
  - Increases excretion of potassium, calcium and magnesium
- Production of copious amounts of urine secondary to dose-dependent diuresis

Loop Diuretics

- **Therapeutic uses**
  - Reduce edema associated with heart failure, kidney disease, or cirrhosis
  - Hypercalcemia (along with hydration)
- **Adverse effects**
  - Ototoxicity (caution with aminoglycosides)
  - Hyperuricemia
  - Acute hypovolemia
  - Potassium depletion
  - Hypomagnesemia
  - Hyperglycemia
  - Caution in sulfa-allergic patients

Loop Diuretics Summary

Drug	Initial Dose	Maximum Dose**
Bumetanide	0.5-1 mg once or twice daily	10 mg daily
Furosemide	20-40 mg once or twice daily	400 mg daily
Torsemide	10-20 mg once or twice daily	200 mg daily

** Titrate to achieve dry weight

Thiazide Diuretics: Mechanism of Action

- Act in the distal tubule to decrease the reabsorption of sodium via inhibition of the Na^+/Cl^- cotransporter
  - Site of action located on luminal membrane, therefore must be secreted into the tubule lumen to be effective
  - Chronic use results in potassium and magnesium losses and decreased urinary calcium excretion
- Reduces blood pressure, cardiac output and peripheral vascular resistance

Thiazide Diuretics

- **Therapeutic uses**
  - Hypertension
    - Generally well-tolerated
    - Inexpensive
    - Once-daily administration
  - Heart failure
  - Hypercalciuria
  - Diabetes insipidus
    - Can produce hyperosmolar urine
- **Adverse effects**
  - Potassium depletion
  - Hyponatremia
  - Hyperuricemia
  - Volume depletion
  - Hypercalcemia
  - Hyperglycemia
  - Hyperlipidemia
  - Caution in sulfa-allergic patients

Summary: Drugs for Symptom Control in Heart Failure

Drug/Class	Adverse Events	Notes
Diuretics	•Hypokalemia •Dehydration •Decreased cardiac output	•Loops usually preferred •More frequent, lower doses better than less frequent, higher doses? •Helps other therapies work better
Digoxin	•Anorexia •Nausea •Vomiting •Arrhythmias •Visual disturbances	•Reduces hospitalization •Low dose therapy

Management of Dyslipidemia in Adults: ATP-4

- Shift towards **A**thero**S**clerotic **C**ardio**V**ascular **D**isease (ASCVD) risk reduction vs. LDL goal
  - Ultimately because there is very little clinical evidence that supports the current goal of < 100 mg/dL in terms of cardiovascular risk reduction
  - Focuses on **statin intensity** and a de-emphasis for the use of non-statin therapies
    - High intensity statins (reduces LDL by up to 60%)
      - Atorvastatin 40-80 mg daily
      - Rosuvastatin 20-40 mg daily
    - Moderate intensity statins (reduces LDL by 30-50%)
      - Atorvastatin 10-40 mg daily or rosuvastatin 5-20 mg daily
      - Pravastatin 40-80 mg daily
      - Simvastatin 20-40 mg daily

Management of High Blood Cholesterol in Adults- ATP-4. *Circulation*. 2014.

Management of Dyslipidemia in Adults

4 major statin benefit groups

1. All patients (≥ 21 years) with any form of CVD or patients with LDL ≥ 190 mg/dL
   - Treat with high intensity statin (ex: atorva 40-80 mg po daily)
   - Goal: reduce LDL-C by > 50%
2. All patients aged 40-75 years with DM and LDL between 70-189 mg/dL WITHOUT CVD
   - Treat with moderate intensity statins (ex: atorva 20 mg po daily)
   - Goal: reduce LDL-C by 30-50%

Management of High Blood Cholesterol in Adults- ATP-4. *Circulation*. 2014.

Management of Dyslipidemia in Adults

3. All patient with LDL 70-189 mg/dL with a 10 year ASCVD risk of > 7.5% should be on a high dose statin therapy
4. All patients with clinical ASCVD (ACS, stroke, TIA, etc.) should be on moderate to high intensity statin regardless of LDL levels

The bottom line:

The new guidelines no longer focus on "the numbers," but instead focus on the reduction of heart disease and stroke risk

Management of High Blood Cholesterol in Adults- ATP-4. *Circulation*. 2014.

10-Year Risk Calculator

- The calculator included in the guidelines aims to gauge an individual's chances of developing atherosclerotic cardiovascular disease (ASCVD) over the next 10 years
- The information required to estimate ASCVD risk includes:
  - Age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status
  - Anyone with a greater than 7.5% chance of having a heart attack or stroke or developing other form of cardiovascular disease in the next 10 years should be started on a high intensity statin therapy
  - The calculator can be found on www.heart.org

Management of High Blood Cholesterol in Adults- ATP-4. *Circulation*. 2014.

Management of Dyslipidemia in Adults

- Monitoring:
  - Initial fasting lipid panel
  - Second lipid panel in 6-12 weeks to determine adherence
  - Follow up in 6-12 months for adherence and safety monitoring
    - LDL levels and % reduction are used only to assess response not clinical outcomes
  - No current evidence suggests that non-statin therapies reduce CV risk
- Take home message:
  - Cardiovascular risk reduction should only be achieved with statins
  - Treatment to LDL goal or attempting to achieve lower LDL levels is no longer recommended

Management of High Blood Cholesterol in Adults- ATP-4. *Circulation*. 2014.

Antilipemic Medications

- Hydroxymethylglutaryl-CoA-reductase inhibitors
  - The "statins"
- Ezetimibe
- Nicotinic acid
- Fibric acid derivatives
- Bile acid binding resins

"Statins"

- 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors
- Drug class of choice
- Agents
  - Atorvastatin (Lipitor®)
  - Fluvastatin (Lescol®)
  - Lovastatin (Mevacor®)
  - Pravastatin (Pravachol®)
  - Rosuvastatin (Crestor®)
  - Simvastatin (Zocor®)
  - Pitavastatin (Livalo®)

"Statins": Administration

- Peak activity of HMG-CoA reductase
  - Midnight
- Administer in the evening
  - Except atorvastatin and rosuvastatin
- Maximal lipid effects: 2 – 4 weeks

"Statins": Safety and Adverse Effects

- Well tolerated
- Rhabdomyolysis
- Proteinuria
- Dose-dependent elevations in hepatic transaminases
- Death*

Ezetimibe

- Inhibits the intestinal absorption of cholesterol
- Adjunct to statin therapy
- 10 mg/day with or without food
- Well tolerated
- Lowers LDL by 18-20%, TG by 5-14%
- Raises HDL by 1-5%

Nicotinic Acid and Niacin

- Used for 40 years
- Decreases production and release of VLDL
- Starting dose 250 mg daily or bid
- Titrate up to 2 – 3 gm daily
- Adverse effects: flushing**, GI upset
- Lowers LDL by 5-25%, TG by 20-50%
- Increases HDL by 15-35%

**Niaspan® – produces less flushing

Fibric Acid Derivatives

- Reduces elevated TG levels and raise HDL
- Lowers TG by increasing lipoprotein lipase activity
- Gemfibrozil and fenofibrate
- Well tolerated
- Lowers TG 20-50%, raise HDL 10-35%

Bile Acid Binding Resins

- Anion exchange resins
- Primarily adjunct to statins
- Cholestyramine, colestipol, colesevelam
- Administer 1 hour before or 4 hours after other medications
- Adverse effects
- Lowers LDL 15-30%

Summary: Lipid Lowering Agents

Drug Class	Lipid Effects	Side Effects	Contra-indications
"Statins"	**LDL** ↓ **HDL** ↑ **TG** ↓	Myopathy Rhabdomyolysis ↑ liver enzymes	Active or chronic liver disease
Bile acid binding resins	**LDL** ↓ **HDL** ↑ **TG** ↑	GI distress Constipation ↓ drug absorption	Dysbeta-lipoproteinemia TG >400 mg/dL
Niacin and nicotinic acid	**LDL** ↓ **HDL** ↑ **TG** ↓	Flushing ↑ blood sugar ↑ uric acid levels Liver damage	Chronic liver disease Severe gout
Fibric acids	**LDL** ↓ **HDL** ↑ **TG** ↓	Dyspepsia Gallstones Myopathy	Severe renal or hepatic disease

Types of Arrhythmias

- Supraventricular arrhythmias- abnormal rate or rhythm originating above and *including AV* node
  - Sinus tachycardia or sinus bradycardia
  - Atrial flutter (1 foci beating irregularly)
  - Atrial fibrillation (multiple foci beating irregularly)
- Ventricular arrhythmias – abnormal rate or rhythm originating below the AV node
  - Non-sustained ventricular tachycardia (V-tach)
    - Self terminating in approx 30 sec.
  - Sustained V-tach (usually doesn't self terminate)
    - Ex: Torsades de Pointe (TdP)
  - Ventricular Fibrillation

Antiarrhythmic Medications: Modified Vaughn-Williams Classification

- Class I – Sodium channel blocking agents
  - Class IA: Quinidine, procainamide
  - Class IB: Lidocaine
  - Class IC: Flecanide, propafenone
- Class II – Beta blocking agents
- Class III – Potassium channel blockers
  - Amiodarone, sotalol
- Class IV – Calcium channel blockers

Antiarrhythmic Medications

Class	Drugs	MOA	Conduction	Refractory Period	Automaticity
IA	Quinidine Procainamide Disopyramide	Na^+ channel blockade (intermediate)	↓	↑	↓
IB	Lidocaine Mexilitine	Na^+ channel blockade (fast)	↓	↓	↓
IC	Flecainide Propafenone	Na^+ channel blockade (slow)	↓↓	No effect	↓
II	Metoprolol Atenolol	Beta-receptor blockade	↓	↑	↓
III	Amiodarone Sotalol Dofetilide Ibutilide	K^+ channel blockade	No effect	↑↑	No effect
IV	Diltiazem Verapamil	Ca^{2+} channel blockade	↓	↑	↓

Class Ia Agents: Disopyramide, Quinidine, Procainamide

- Intermediate sodium channel blockade
  - Slow conduction velocity
  - Prolong refractoriness
  - Decrease the automatic properties of sodium-dependent conduction tissue
- Effective for SVTs and ventricular arrhythmias (procainamide only)

Quinidine and Drug Interactions: CYP 3A4 substrate

- Warfarin → increased INR
- Digoxin → increased digoxin levels
- Quinidine levels are decreased by:
  - Phenobarbital, rifampin, phenytoin
- Quinidine levels increased by amiodarone
- Should not be used with agents that prolong the QTc interval
  - Moxifloxacin, erythromycin, haloperidol, etc.

Adverse Effects

- **Disopyramide**
  - Anticholinergic symptoms
  - GI
  - Proarrhythmia
- **Procainamide**
  - GI – nausea, vomiting, diarrhea
  - Agranulocytosis
  - Drug-induced lupus (20 %)
    - Fever, rash, arthritis, pleuritis, or pericarditis with long term use
  - Proarrhythmia
- **Quinidine**
  - GI (especially, diarrhea)
  - Dizziness
  - Headache
  - Cinchonism
    - Tinnitus, visual blurring and hearing disturbances
  - Hemolytic anemia
  - Rash
  - Thrombocytopenia

Class Ib Agents: Lidocaine, Mexiletine, Phenytoin

- Fast on-off sodium channel block
  - Little effect on rapid sodium channels at normal heart rates
  - Decrease the duration of the action potential by shortening repolarization
- At fast heart rates, during ischemia, hypokalemia, or acidosis slows depolarization and conduction velocity
- Little effect on atrial tissue and left ventricular function
- Indicated for ventricular arrhythmias

Class Ic Agents: Flecainide and Propafenone

- Effective in both atrial and ventricular arrhythmias
- Pronounced effect on slow sodium channels
- Slow conduction even at normal heart rates
- Refractoriness is relatively unchanged
- Torsades is a MAJOR concern

Class II Agents: Beta Blockers

- Mechanism related to anti-adrenergic effects
- SA and AV nodes are heavily influenced by adrenergic activity
- Beta stimulation
  - Increased conduction velocity
  - Shortened refractoriness
  - Increased automaticity of nodal tissue

} **Antagonized by beta blockers**

Class III Agents: Amiodarone, Sotalol, Dofetilide, Ibutilide

- Prolong the duration of the action potential
  - Block potassium channels that mediate repolarization
  - Increase the refractoriness of atrial and ventricular tissue
- None of these drug are pure Class III agents
  - All act slightly differently depending on their non-Class III effects

Amiodarone

- **Clinical use**
  - Atrial and ventricular tachyarrhythmias
    - Preferred agent in patients with decompensated heart failure vs. beta blocker
- **Mechanism of action**
  - Primary mode = Class III effect (prolongs repolarization): increases QT interval
  - Exhibits all 4 Vaughn Williams effects
- **Clinical effects**
  - Slows SA and AV nodal conduction
  - Slows conduction in ventricular tissue

Amiodarone: Pharmacokinetics

- Absorption : 30-70%; 4-5 h delay in peak levels
- Distribution: 66L/kg
- Metabolism: hepatic
- T1/2: weeks to months
- Drug interactions: many
  - Inhibits P glycoprotein and CYP 3A4
- Dosing schemes: dependent on clinical need and previous dosing history

Amiodarone Side Effects

- Gastrointestinal
- Pulmonary
  - Pneumonitis/fibrosis (acute and chronic)
- Thyroid
  - Hypothyroidism (10%)
  - Hyperthyroidism
  - Contraindicated in thyroid disease
- Cardiac
  - Bradycardia
  - Hypotension (with IV)
- Photosensitivity
  - Blue-gray discoloration of sun exposed skin
- Neurological
  - Ataxia, tremor, sleep disturbance, peripheral neuropathy
- Ocular
  - Poor night vision
  - Corneal micro-deposits

Dronedarone (Multaq®)

- **Mechanism of action**
  - Unknown; has properties of all four Vaughan-Williams classes
- **Indications for use**
  - Reducing hospitalizations for atrial fibrillation
  - For patients with a history of paroxysmal or persistent atrial fibrillation
- **Warnings**
  - Contraindicated in permanent atrial fibrillation or symptomatic heart failure
  - Post-marketing reports of liver injury
  - If QTc interval increases ≥500 ms, discontinue drug

Dofetilide (Tikosyn®)

- Class III Antiarrhythmic
- Indications:
  - Maintenance of NSR in patients with atrial fibrillation/flutter
- Common Side Effects:
  - Headache
  - Chest pain
  - *Scr increase*
- Dosing:
  - *Dose reduction for increase in QTc level or renal dysfunction*
- Serious Adverse Effects:
  - *QTc prolongation*
  - *Torsade de pointes*
- A 3-day hospitalization is mandatory for initiation
  - Monitor: Scr, QTc, Mg, K

Sotalol

- Non-selective beta-blocker in addition to K^+ channel blocker
- Eliminated renally hence dose adjustments are needed
- Initiation requires hospitalization with cardiac monitoring (similar to dofetilide)
- Adverse effects
  - QT-prolongation, Bronchospasm, other Beta-blocker S/E
- Contraindications:
  - QT interval > 450 msec
  - CrCl < 40 mL/min
  - K^+ < 4 mEq/L

Class IV Agents: Calcium Channel Blockers

- Interference with inward calcium flux
  - Inhibits myocardial and vascular smooth muscle contraction
  - May slow AV conduction and SA rate
- Decrease afterload, contractility, heart rate, and improve myocardial blood flow
- Agents differ in these activities

Calcium Channel Blocker: Adverse Events

- Constipation
- Bradycardia, heart block, heart failure
  - Especially in patients treated with BBs
  - Contraindicated in patients with MI and HF
- Hypotension
- Many drug interactions
  - Mediated by CYP enzymes and P glycoprotein

Antiarrhythmics and Drug Interactions

- **CYP 3A4 substrates**
  - Quinidine, disopyramide
  - Lidocaine
  - Propafenone
  - Amiodarone, dofetilide
  - Verapamil, diltiazem
- **CYP 3A4 inhibitors**
  - Amiodarone
  - Verapamil, diltiazem
  - Cimetidine
  - HIV protease inhibitors
  - Itraconazole, ketoconazole
  - Macrolides (*not azithromycin)*

Burden of Atrial Fibrillation (AF)

- Prevalence of AF in the US ~ 2.2 million
- Incidence > 70,000 anually
- Risk of stroke is increased 5-fold
- Severity of stroke is greater in patients with AF
  - Increased mortality 1.8 times higher compared to patient without AF

Lloyd-Jones DM, et al. *Circulation* 2004;110:1042–1046.
Savelieva et al. *Ann Med* 2007;39:371–391.
Hart R et al. *JACC* 2000; 35:183-187.

Rate vs. Rhythm Control

Factors favoring rate:

- Persistent AF
- Less symptoms
- Age >64 years old
- Hypertension
- No history of HF
- Previous failure of antiarrhythmic drug
- Patient preference

Factors favoring rhythm:

- Paroxysmal AF or newly detected AF
- More symptoms
- Age <65 years old
- No hypertension
- HF exacerbated by AF
- No previous failure
- Patient preference

Kamrul R. CFP 2013; 59:161-8.

Rate vs. Rhythm Control

- **Rate control** medications are **safer** in their side effect profiles
- Use of antiarrhythmics for **rhythm control** is associated with **more adverse effects** than rate control
  - Bradycardia
  - QT-prolongation (can be life threatening)
  - Bleeds/gastrointestinal events
    - Due to the use of thromboembolic prophylaxis agents needed prior to most cardioversions

Guidelines for Management of patients with atrial fibrillation. *Circulation*. 2011;123:104-123.

Role of Antiarrhythmics in Atrial Fibrillation

- Pharmacologic cardioversion
  - Primary method to achieve NSR
    - Flecainide, propafenone, ibutilide, dofetilide
    - Amiodarone
  - Adjunct to Direct Current Cardioversion (DCC)
- Maintenance therapy
  - Intermittent
  - Continuous

Patient Case

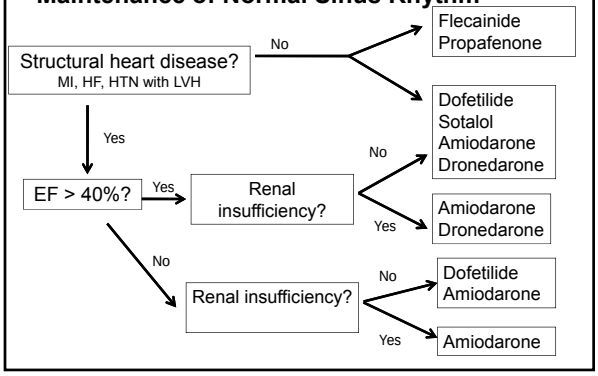
A 75-year-old woman has a history of NYHA class III HF (left ventricular ejection fraction [LVEF] 25%) and several NSTEMIs. She has an episode of sustained ventricular tachycardia (VT) during this hospitalization for pneumonia. Her corrected QT (QT_c) interval was 380 milliseconds on the telemetry monitor and her serum K^+ and Mg^{2+} were 4.6 mEq/L and 2.2 mg/dL, respectively.

PROPERTIES

On passing, 'Finish' button:	Goes to Next Slide
On failing, 'Finish' button:	Goes to Next Slide
Allow user to leave quiz:	At any time
User may view slides after quiz:	At any time
User may attempt quiz:	Just Once

Properties... Edit in Quizmaker

Maintenance of Normal Sinus Rhythm



Anticoagulation in Atrial Fibrillation

- Given medical history, determine risk factors for stroke
  - $CHADS_2$ or $CHADS_2$-VASc
- Given patient's risk score, determine antithrombotic therapy

$CHADS_2$ Score = 0	$CHADS_2$ Score = 1	$CHADS_2$ Score ≥ 2
ACCF/AHA/HRS 2011: No therapy or aspirin 81-325 mg/day	Warfarin (INR 2-3) or aspirin 81-325 mg/day	Warfarin (INR 2-3)
ACCP (Chest) 2012: No therapy or aspirin 81-325 mg/day	Dabigatran 150 mg twice a day over warfarin (INR 2-3)	Dabigatran 150 mg twice a day over warfarin (INR 2-3)
AHA/ASA nonvalvular atrial fibrillation (2012): No therapy or aspirin 81-325 mg/day	Oral anticoagulant (INR 2-3) or aspirin	Warfarin (INR 2-3) Dabigatran Apixaban Rivaroxaban
High-risk patients not considered candidates for anticoagulation: aspirin + clopidogrel		

Warfarin (Coumadin®, Jantoven®)

- **Mechanism of Action**
  - Inhibits factors VII, IX, X, II, and proteins C&S
  - INR goal 2-3, dosing varies
- **Reversal**
  - Phytonadione (vitamin K)
- **Counseling**
  - Consistent vitamin K intake
  - Limit alcohol intake
  - Take dose at same time everyday
  - Signs and symptoms of bleeding
  - Drug Interactions

Target-Specific Oral Anticoagulants (TSOACs)

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto©)	Apixaban (Eliquis©)
Mechanism of Action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Onset of action	Rapid	Rapid	Rapid
Metabolism	Hepatic glucuronidation P-gp substrate	CYP3A4/5 CYP2J2 P-gp substrate	CYP3A4/5 P-gp substrate
Protein Binding	35%	92-95%	87%
Half-life	12-17 hours	5-9 hours 11-13 hours in elderly	12 hours
Renal clearance	80%	35%	27%
Dialyzable	62 – 67%	No	No

Pradaxa® (dabigatran) package insert. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT, 2013.; Xarelto® (rivaroxaban) package insert. Janssen Pharmaceuticals, Inc.Titusville, NJ, 2013. Eliquis® (apixaban) package insert. Bristol-Myers Squibb Company. Princeton, NJ, 2012.; Heidbuchel H, et al. *Europace*. 2013;15:625-651.

FDA-Approved Indications and Dosing

	Indications	Dosing**
Dabigatran (Pradaxa®)	To reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	150 mg po bid
Rivaroxaban (Xarelto®)	To reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	20 mg po qd
	To treat deep vein thrombosis (DVT), pulmonary embolism (PE), and to reduce risk of recurrence of DVT and PE	15 mg po bid for 21 days, then 20 mg po qd for remainder of treatment duration
	DVT and PE prophylaxis in patients undergoing knee or hip replacement surgery	10 mg po qd for 35 days (hip) or 12 days (knee)
Apixaban (Eliquis®)	To reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	5 mg po bid

**See next slide for dosage adjustments

Pradaxa® (dabigatran) package insert. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT, 2013.
Xarelto® (rivaroxaban) package insert. Janssen Pharmaceuticals, Inc.Titusville, NJ, 2013.
Eliquis® (apixaban) package insert. Bristol-Myers Squibb Company. Princeton, NJ, 2012.

When are Dosage Adjustments Necessary?

	Dosage Adjustments
Dabigatran (Pradaxa®)	CrCl > 30 mL/min: 150 mg po bid CrCl 15-30 mL/min: 75 mg po bid CrCl < 15 mL/min: contraindicated
Rivaroxaban (Xarelto®)	Stroke and systemic embolism in patients with nonvalvular atrial fibrillation: CrCl > 50 mL/min: 20 mg po qd CrCl 15-50 mL/min: 15 mg po qd CrCl < 15 mL/min: avoid use
	Treatment of DVT, PE and risk reduction of DVT and PE recurrence: no adjustment needed CrCl > 30 mL/min: 15 mg po bid for 21 days for treatment, then 20 mg qd to reduce risk of recurrence CrCl < 30 mL/min: avoid use
	DVT and PE prophylaxis after hip or knee replacement surgery: no adjustment needed CrCl > 30 mL/min: 10 mg po qd CrCl < 30 mL/min: avoid use
Apixaban (Eliquis®)	2.5 mg po bid in patients with at least two of the following characteristics: ≥ 80 years old, ≤ 60 kg, SCr ≥ 1.5 mg/dL

Pradaxa® (dabigatran) package insert. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT, 2013.
Xarelto® (rivaroxaban) package insert. Janssen Pharmaceuticals, Inc.Titusville, NJ, 2013.
Eliquis® (apixaban) package insert. Bristol-Myers Squibb Company. Princeton, NJ, 2012.

Which TSOAC Do I Choose for Stroke Prevention in NVAF?

Characteristic	Drug Choice(s)	Rational
Mechanical valve or valvular AF	Warfarin	Lack of data with TSOACs
Liver dysfunction with elevated INR	Warfarin	New agents require hepatic metabolism
Poor compliance	Warfarin or nothing	Missed doses are a bigger issue with TSOACs
Poor compliance due to medication regimen complexity	Rivaroxaban	Simply regimen and follow-up
CrCl < 15 mL/min (< 30 mL/min?)	Warfarin	Patients with severe renal disease were excluded from trials
Dyspepsia	Rivaroxaban or apixaban	Dyspepsia occurred in up to 10% of dabigatran users
Recent GI bleed	Apixaban	Lower GI bleed risk
Recent stroke on warfarin	Dabigatran	Lower ischemic stroke risk in RE-LY
Recent ACS	Rivaroxaban or apixaban	MI signal with dabigatran

Schulman S et al. *Blood* 2012;119(13):3016-23

Thank you!

Resources

- Predicting cardiovascular drug interactions: http://circ.ahajournals.org/cgi/reprint/101/14/1749
- 2013 ACC/AHA Dyslipidemia Guidelines: https://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a
- 2013 ACC/AHA Heart Failure Guidelines: http://circ.ahajournals.org/content/128/16/e240.short?rss=1&ssource=mfr
- JNC VIII Hypertension Guidelines: http://jama.jamanetwork.com/article.aspx?articleid=1791497
- At what level of hyperkalemia or creatinine elevation should ACE inhibitor therapy be stopped or not started? http://www.ccjm.org/pdffiles/Nurkomin901.pdf