Antiarrhythmic drugs: Pearls for practice

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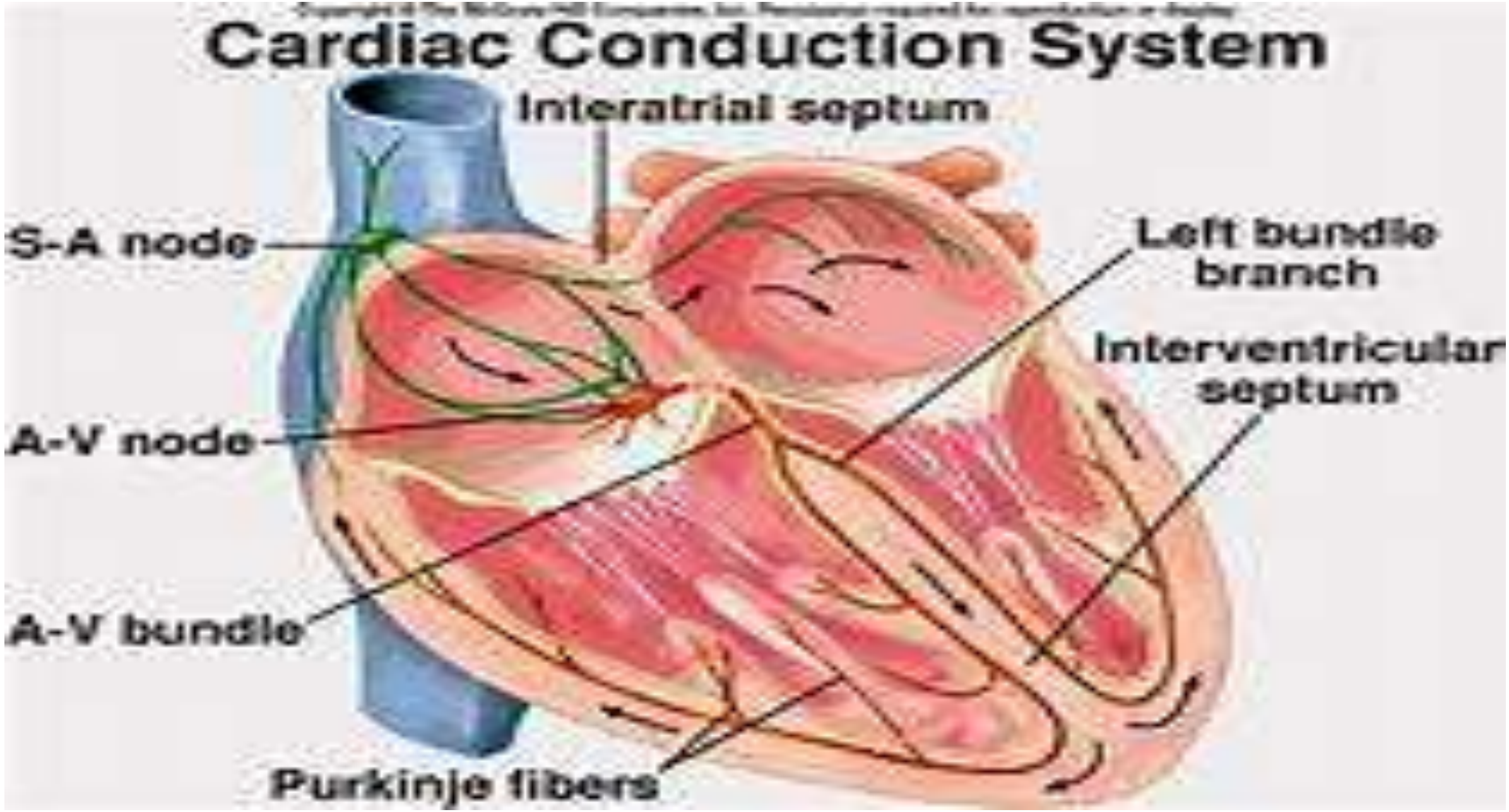
No financial disclosures

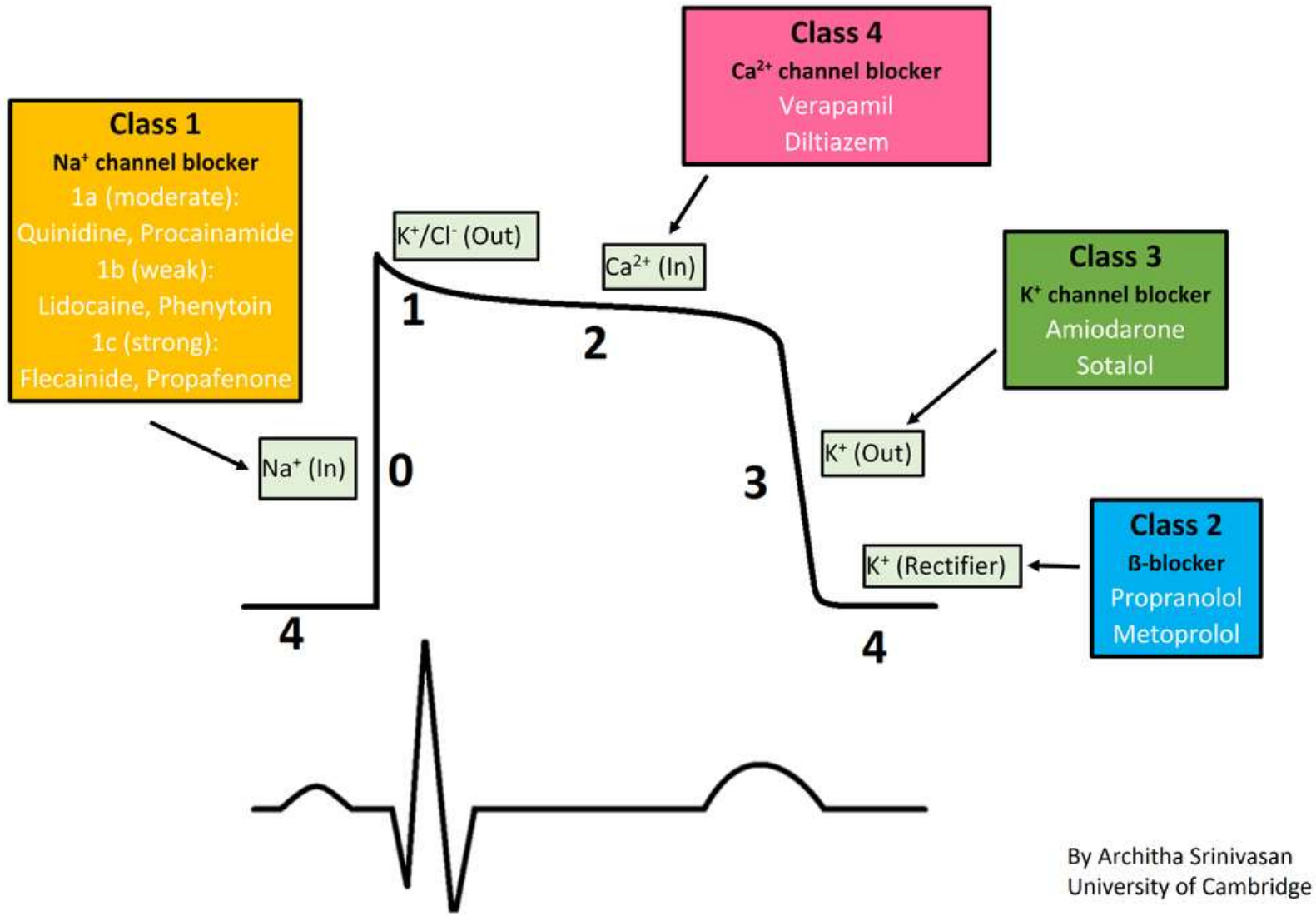
Objectives

- Review EKG basics
- Understand Vaughn Williams antiarrhythmic drug classes
- Correlate atrial arrhythmias
- Distinguish ventricular arrhythmias
- Learn future of AAD
- References
- Questions


Cardiac Conduction System
Interatrial septum
S-A node
A-V node
A-V bundle
Purkinje fibers
Left bundle branch
Interventricular septum

		General Mechanism	Effect on Action Potential	Examples	Additional "Extraclass" Actions	Major or Unique Side Effects / Toxicity	Common Antiarrhythmic Indications
I	Ia	Na^+ channel blocker	↓↓ upstroke rate ↑ AP duration	Quinidine Procainamide	Class III activity	• Prolonged QT • Quinidine: Cinchonism • Procainamide: Drug-induced lupus	• Quinidine: Brugada synd. • Procainamide: AVRT and preexicted a-fib & a-flutter
	Ib		↓ upstroke rate ↓ AP duration	Lidocaine (IV only) Mexiletine	None	Various CNS effects (predom. lidocaine)	Suppression of VT (typically in acute ischemia)
	Ic		↓↓↓ upstroke rate ∅ AP duration	Propafenone Flecainide	Class II activity *(propafenone only)*	Increased risk of death when used in patients post-MI.	Maint. of sinus rhythm in paroxysmal a-fib (PAF), (but only if no CAD/HF)
II		β blocker	Slows rate of depolarization in slow AP cells	Metoprolol Esmolol (IV only) Acebutolol Pindolol	None *(among these β blockers)*	• Bronchospasm • Depression • Exercise intolerance • Sexual dysfunction	• Rate control of a-fib/flutter • Suppression of PVCs, PACs, and VT
III		K^+ channel blocker	↑↑↑ AP duration	Amiodarone	Class I, II, and IV activity	• Pulmonary fibrosis • Thyroid disease • Hepatic dysfunction, ↑ LFTs	• Cardioversion of a-fib/flutter • Maintenance of sinus rhythm in PAF • Suppression of VT
				Dronedarone	Class I, II, and IV activity	• Prolonged QT • Contraindicated in permanent a-fib, and decompensated heart failure	Maintenance of sinus rhythm in PAF
				Sotalol	Class II activity	Prolonged QT	• Maintenance of sinus rhythm in PAF • Suppression of VT
				Dofetilide	None	Prolonged QT	• Cardioversion of a-fib/flutter • Maintenance of sinus rhythm in PAF
IV		Ca^{2+} channel blocker	Slows rate of depolarization in slow AP cells	Verapamil Diltiazem	Vasodilation	Negative inotropy	• Rate control of a-fib/flutter • Prevention of AVNRT
Digoxin		↑ vagal tone, Inhibits Na^+/K^+ pump	Slows rate of depolarization in slow AP cells	N/A	Strengthens myocardial contraction	Very proarrhythmic	Rate control of a-fib (2nd line)
Adenosine		Induces AV block	↑ refractory period ↑ threshold potential ↓ upstroke rate	N/A	Vasodilation	"Dying-like" sensation	• Termination of AVNRT, AVRT • "Uncovering" a-flutter, AT

Drugs Affecting the Cardiac Action Potential



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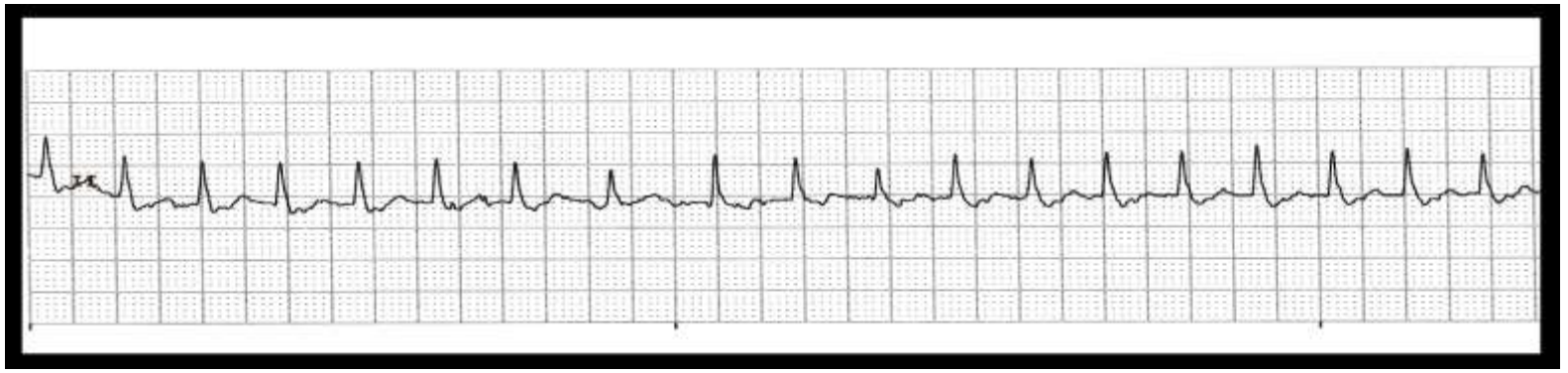
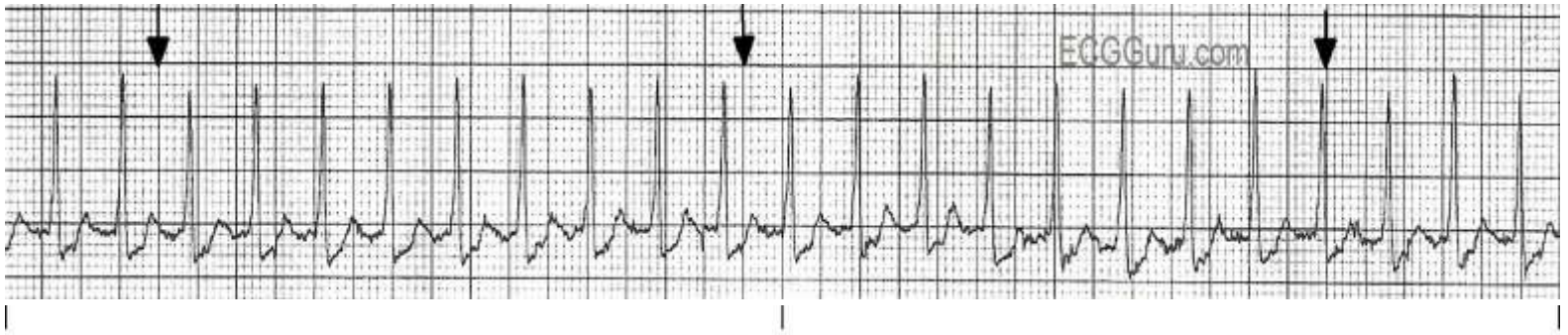
Atrial arrhythmias

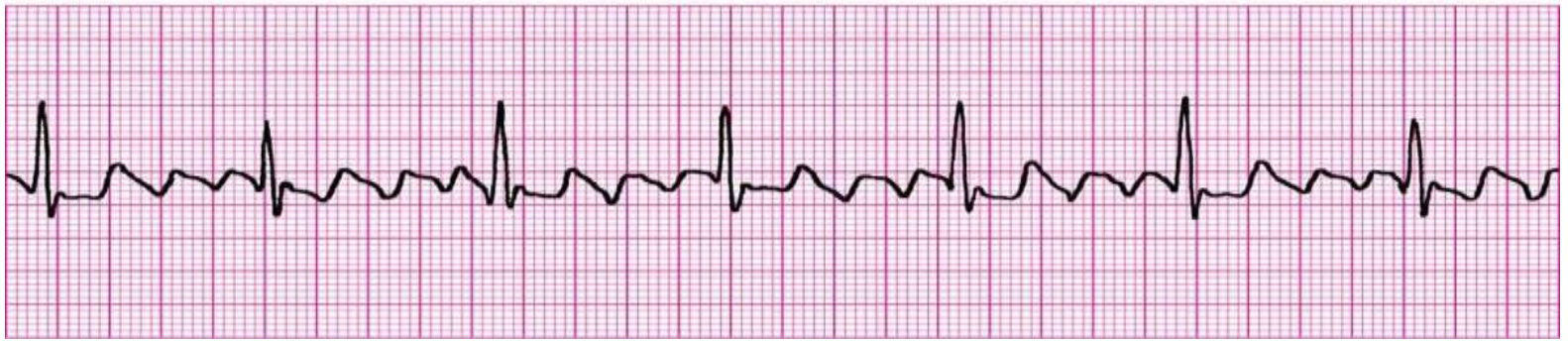
Atrial fibrillation

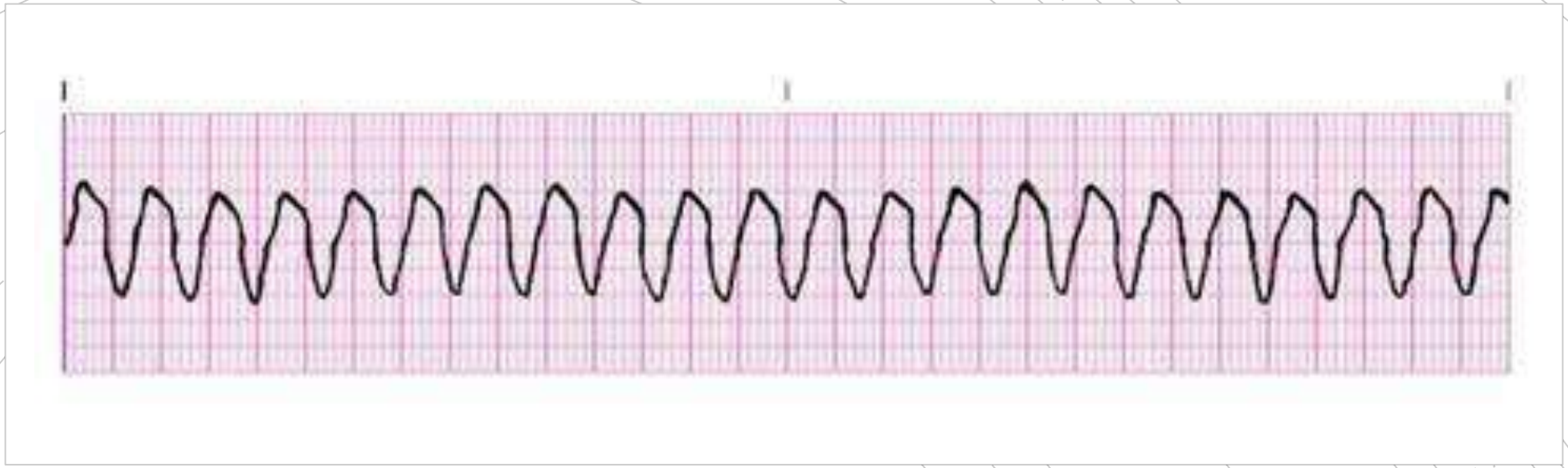


Supraventricular Tachycardia



Atrial flutter

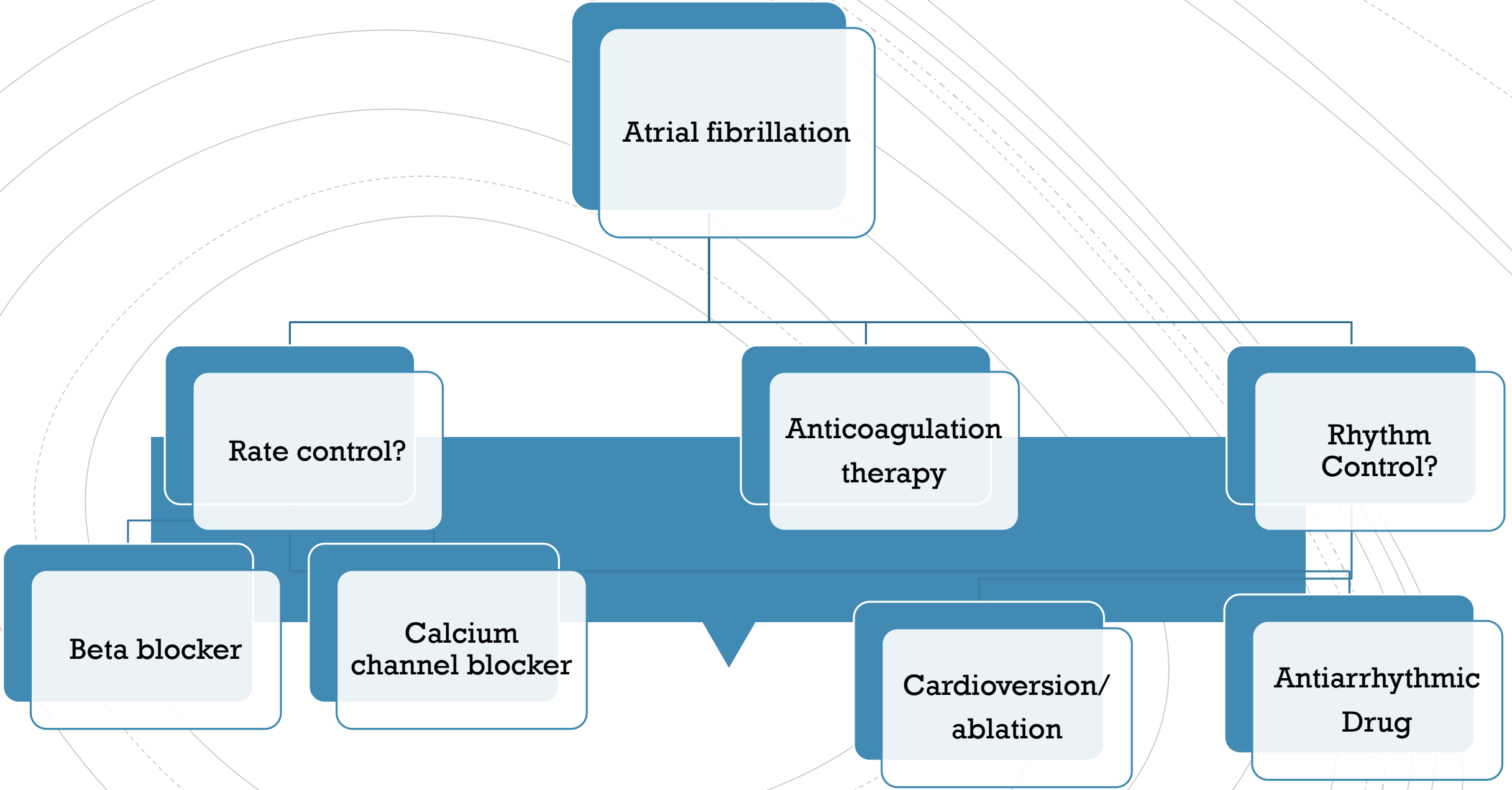




Ventricular tachycardia

Rate vs rhythm control?

- 88-year-old male presents to PCP for annual check up. He has no complaints or concerns. He is found to be in atrial fibrillation with RVR ventricular rate 123 bpm. BP 145/88 mmHg. RR 16. BMI 39. He has a history of T2DM, CKD stage 3b (CrCl 35), COPD, HTN, dyslipidemia. Echo 3 years ago: LVEF 50%, grade II diastolic dysfunction, mild aortic valve stenosis. Prescription medications: metformin 500 mg BID, lisinopril 5 mg daily, hydrochlorothiazide 25 mg daily, simvastatin 20 mg daily & albuterol inhaler prn.
- He is completely asymptomatic and shocked to learn his heart rate is so high
- You discuss EP referral, cardioversion, AD and possible ablation
- Patient and family are adamant: no intervention! Together you decide on anti-coagulation therapy and rate control approach


Atrial fibrillation
Rate control?
Anticoagulation therapy
Rhythm Control?
Beta blocker
Calcium channel blocker
Cardioversion/ ablation
Antiarrhythmic Drug

Class II & Class IV Antiarrhythmic Drugs

CLASS II BETA BLOCKERS

- Beta 1
  - Propranolol
- Beta 2 Cardio Selective
  - Atenolol
  - Metoprolol tartrate
  - Metoprolol succinate

CLASS IV CALCIUM CHANNEL BLOCKERS

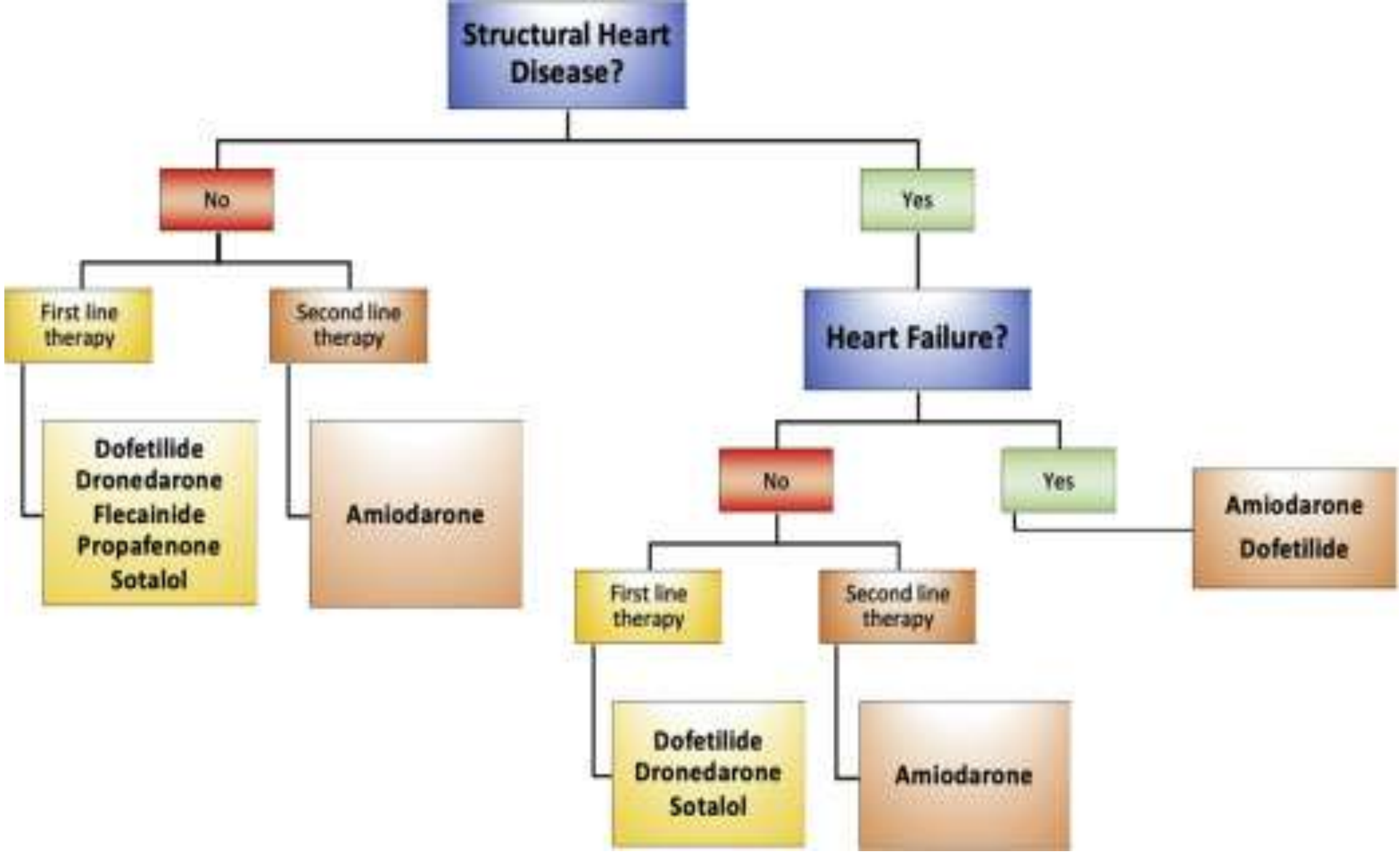
- Diltiazem
- Diltiazem SR
- Verapamil

Digoxin

- Mechanism of action
  - Decrease SA node activity
  - Decrease AV conduction velocity
  - Increase PRI
  - Increase QT interval
  - Increase vagal activity

Rate or Rhythm Control?

- 52-year-old male recently diagnosed with new onset afib. Underwent successful direct current cardioversion 3 weeks ago from afib to NSR. Today he complains of irregular heart beats, dyspnea, fatigue and lightheadedness for the last 4 days. EKG shows atrial fibrillation with controlled ventricular rate. He has a history of morbid obesity, hypertension, type 2 diabetes mellitus, sleep disturbance and sedentary lifestyle. VS: HR 97 bpm, BP 138/86 mmHg, BMI 39. Recent nuclear stress treadmill was negative for ischemia. Ejection fraction 55%. Normal kidney function. Medications: Xarelto 20 mg daily, metoprolol succinate 50 mg BID, losartan 25 mg daily.


Structural Heart Disease?
No
Yes
First line therapy
Second line therapy
Dofetilide
Dronedarone
Flecainide
Propafenone
Sotalol
Amiodarone
Heart Failure?
No
Yes
Amiodarone
Dofetilide
First line therapy
Second line therapy
Dofetilide
Dronedarone
Sotalol
Amiodarone

Class 1C

Sodium channel blockers

INDICATIONS

- Atrial fibrillation
- Atrial arrhythmias
- Ventricular ectopy

MECHANISM OF ACTION

- Slow conduction velocity
- Prolongs Phase 0 Ventricular action potential
- Prolongs QRS duration

Class 1C Fast sodium channel blockers – Key Notes

Must be partnered with AV blocking agent!

Increased risk of atrial flutter

Adverse Effects

Pro-arrhythmia

Dizziness/lightheadedness

Headache

Fatigue

Tremor

Blurry vision

Contraindications

Structural Heart Disease
Heart Failure

Pregnancy

Fetal risk cannot be ruled out

Class IC Antiarrhythmic Drug Interactions

- Phenobarbital
- Phenytoin
- Rifampin
- Quinidine
- Cimetidine
- Digoxin
- Propranolol
- Theophylline
- Cyclosporine
- Desipramine

Flecainide (Tambocor)

Pharmacokinetics

- Absorption
  - Systemic – food effects none
- Metabolism
  - Hepatic via P450
  - CYP2D6 pathway
- Elimination half life
  - 20 hours

Dosages

- 50-150 mg BID – maintenance
- 300 mg - pill in the pocket

Propafenone (Rhythmal)

Pharmacokinetics

- Absorption
  - Gastrointestinal tact
- Metabolism
  - Hepatic
- Elimination half life
  - 6-7 hours
  - 3 days to reach steady state

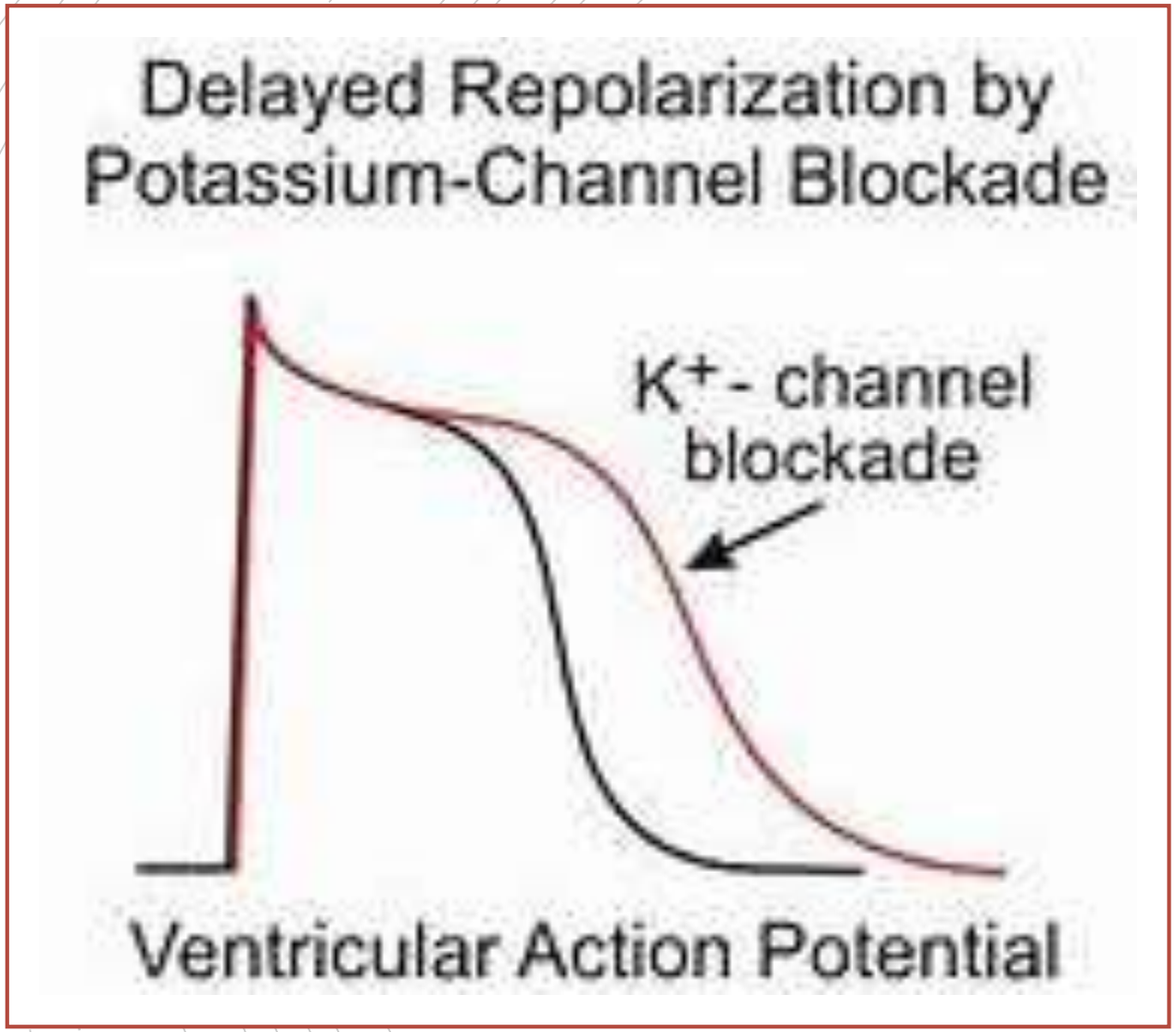
Dosages

- 150-300 mg TID
- 600 mg – Pill in the Pocket

Case study

60-year-old female with symptomatic persistent atrial fibrillation. She has a history of pulmonary vein isolation cryoablation and redo radiofrequency ablation x 2 for afib and atrial flutter. Stress test is negative. Normal blood pressure, liver and kidney function.
Weight is within normal limits. She has a significant history of anxiety. She is normal weight. No structural Heart disease

She has a history of failed flecainide and propafenone therapy.



Class III Potassium channel blockers

Indications	Mechanism of Action
• Atrial fibrillation • Atrial flutter • Supraventricular tachycardia • Ventricular arrhythmia	• Prolongs phase 3 action potential • Prolongs outflow of K+ • Prolongs refractoriness

Adverse Effects

- Cardiovascular
  - Chest pain 10% - common
  - Heart block – rare
  - Prolonged QT interval - rare
  - Ventricular arrhythmia – rare
- Neurologic
  - Dizziness 8%
  - Headache 11%
- Generalized
  - Nausea, abdominal pain, flatulence, diarrhea, fatigue

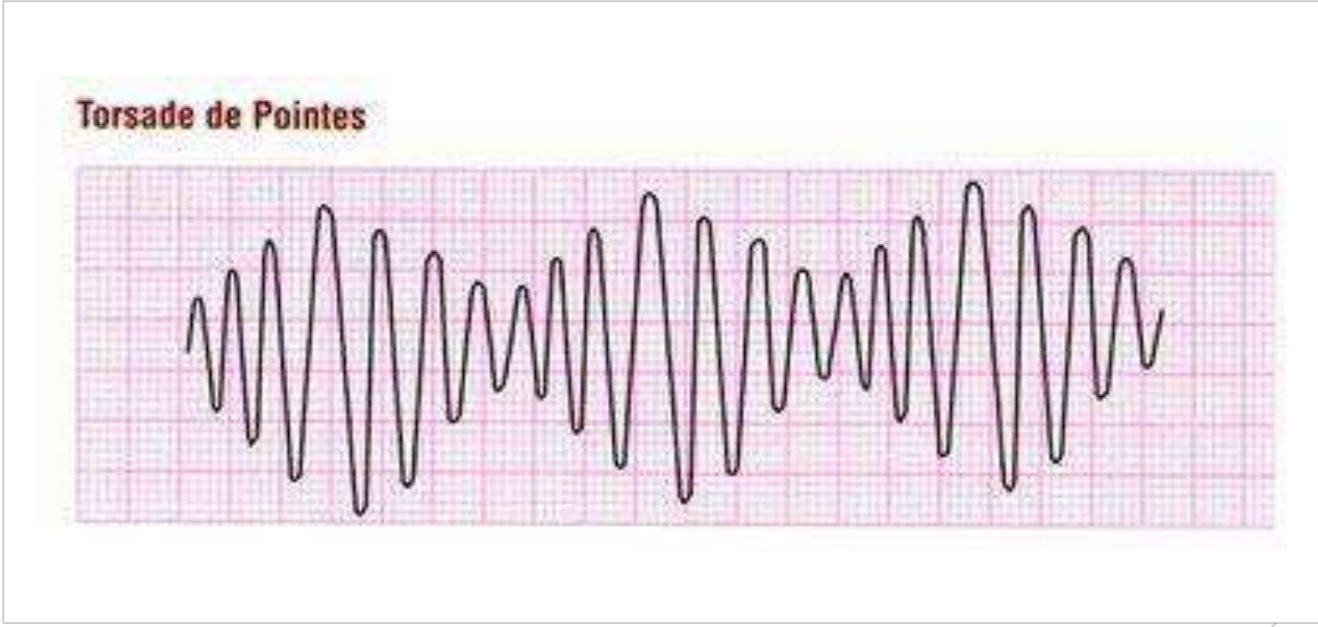
Class III Potassium channel blockers

Torsades de Pointes

Dofetilide (Tikosyn) & Sotalol (Betapace)

3-Day hospital induction with telemetry monitoring x 5 doses

- K+: > 4.0
- Mg: > 2.0
- QTc: < 450 ms in general
- QTc with ventricular conduction abnormality: < 500 ms
- CrCl: >40 ml/min



Dofetilide (Tikosyn)

- Pharmacokinetics
  - Absorption
    - Systemic – food effects none
  - Metabolism
    - Hepatic via CYP3A4 pathway
  - Excretion
    - Renal (70-80%)
  - Elimination half life
    - 10 hours
  - Dosages
    - 250-500 mcg BID (250 mcg for CrCl 20-59 ml/min)

- Contraindications
    - Renal insufficiency
    - Long QTc

Dofetilide drug interactions

- Cimetidine (Tagamet®).
- Cisapride (Propulsid®).
- Verapamil (Calan®, Covera-HS®, Isoptin®, others).
- Ketoconazole (Nizoral®).
- Itraconazole (Sporanox®).
- Trimethoprim (Proloprim®, Primsol®, others).
- Hydrochlorothiazide
- Sotalol (Betapace®).
- Ziprasidone (Geodon®).
- Amitriptyline (Elavil®) or other tricyclic antidepressants.
- Promethazine (Phenergan®).
- Prochlorperazine (Compazine®).
- Quinidine (Quinaglute®, Quinidex Extentabs®, others).
- Disopyramide (Norpace®).

Cleveland Clinic, 2020)

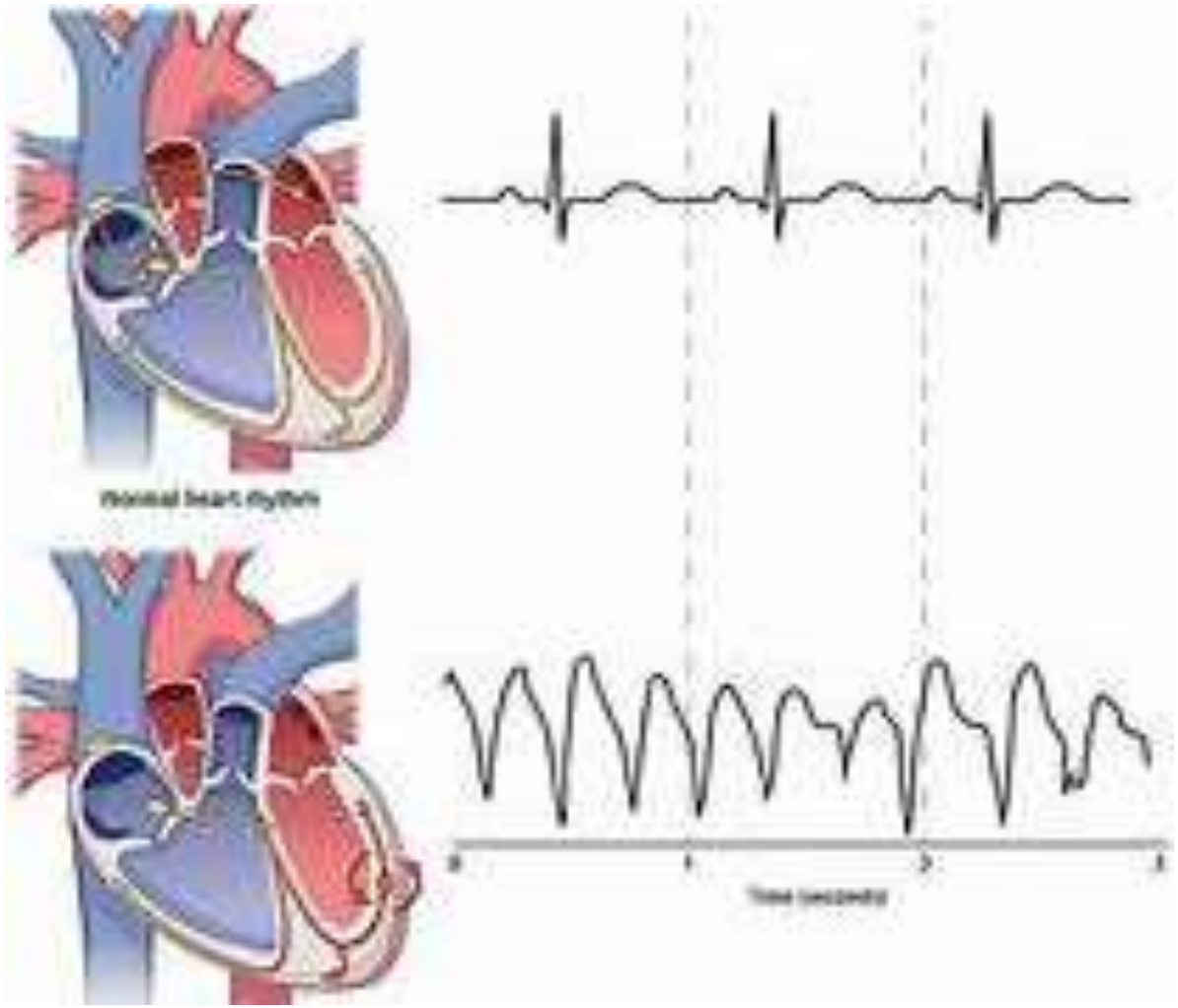
Sotalol (Betapace)

- Pharmacokinetics
  - Absorption
    - Oral – food reduces absorption
  - Metabolism
    - Liver
  - Excretion
    - Renal
  - Elimination half life
    - 12 hours
  - Dosages
    - 80 mg BID

Contraindications

- Renal insufficiency
- Bronchial asthma or bronchospastic conditions
- Negative inotropic effects

Case study



70 yo female
presents with recurrent ICD shocks.

- PM interrogation
  - Nonsustained ventricular tachycardia
- Medical history
  - Biventricular ICD implantation
  - Type 2 diabetes mellitus
  - Chronic kidney disease
  - CAD/myocardial infarction with stent insertion
  - Heart failure with reduced ejection fraction – LVEF 30%

Amiodarone (Cordarone)

- ***Formulated with 40% iodine***

- Pharmacokinetics
  - Absorption
    - Systemic – food significantly enhances
  - Metabolism
    - Hepatic via N-deethytation
  - Excretion
    - Primary bile
  - Elimination half life
    - Oral - 26-107 days
  - Dosages
    - Loading 200 mg BID -QID x
    - Maintenance 100-200 mg daily

Amiodarone Precautions/monitoring

Cardiovascular – bradycardia, hypotension, prolonged QT interval

- Monitor – 12-lead EKG QTC >550 ms

Dermatologic – photosensitivity, blue-gray skin discoloration

Endocrine - hyper/hypothyroidism, thyroid nodules, thyroid cancer

- Monitor – TSH, Free T4

Hepatic – hepatocellular necrosis, acute renal failure

- Monitor – LFTs

Ophthalmic – optic neuropathy, corneal microdeposits

- Monitor – ophthalmology exam

Respiratory – pneumonitis, pulmonary toxicity, pulmonary fibrosis

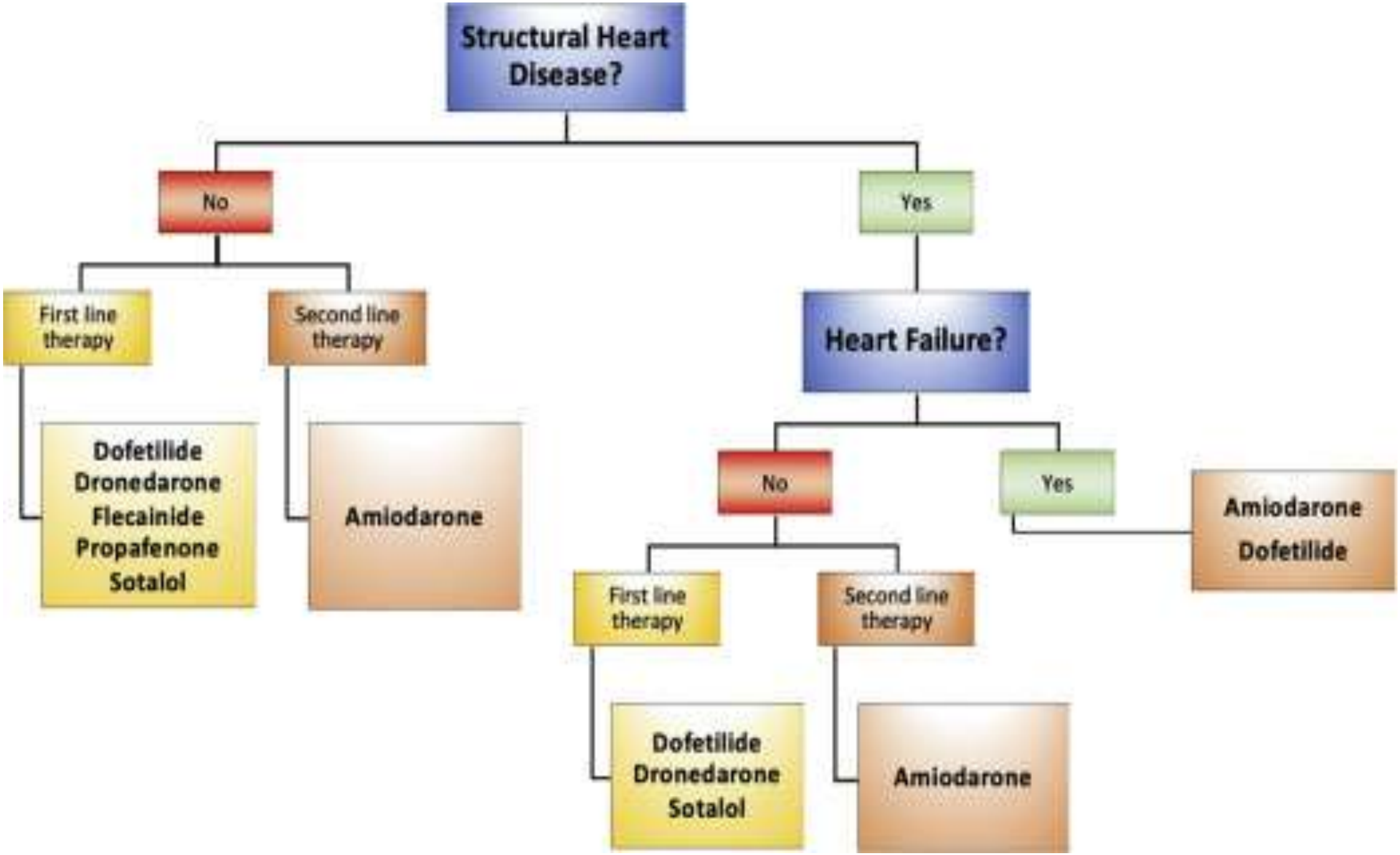
- Monitor – chest x-ray, PFTs

Amiodarone drug interactions

- Increases potentiation
  - Warfarin
  - Digoxin
  - Beta blockers
  - Calcium channel blockers
  - Quinidine
  - Procainamide
  - Phenytoin
  - flecainide

The future of Antiarrhythmic Drugs

- Vaughn-Williams classification increase from V to VII
  - VI - Gap-junction channel inhibitors
  - VII - Upstream target modulators
- Ranolazine (Ranexa) HARMONY TRIAL
  - Antianginal
  - Reduces AF incidence
- Class VII Upstream target modulators
  - ACE/ARBs
    - HF GDMT by ACCF/AHA
    - Decreased AF incidence by 28% in LV dysfunction/hypertrophy
  - Spironolactone/eplerenone
    - Decreased sudden death and VT by 21% & 72%
    - With or without heart failure
  - Omega 3 fatty acids
    - Decrease AF after CABG
  - Statins – 62 studies
    - Decrease recurrent AF 3 months after DCCV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Amiodarone
Heart Failure?
No
Yes
Amiodarone
Dofetilide
First line therapy
Second line therapy
Dofetilide
Dronedarone
Sotalol
Amiodarone

Case study 1

- 35-year-old male with no cardiac history, fairly-active, 8 hours after heavy alcohol drinking at a wedding no afib history
- ED
  - EKG: atrial fibrillation with RVR, Vent rate 170 bpm
  - Vital signs: BP 168/88 mmHg, HR 177 bpm, RR 22 pm
  - Presenting symptoms: lightheadedness, chest discomfort, fatigue, dyspnea
  - Diltiazem IVP then oral
  - Spontaneously converted
  - Echo: LVEF 65%, no structural heart disease
- Referred to primary care provider
  - No further symptoms except anxiety
  - Vital signs: BP 125/76 mmHg, HR 62 bpm, RR 16 pm, BMI wnl
  - EKG: NSR, Vent rate 72 bpm, PRI 180 ms, QRS 98 ms, QTc 401 ms

Question 1

- What would you order?
  - A. metoprolol succinate 25 mg daily
  - B. flecainide 300 mg pill in the pocket
  - C. Counsel patient on detriments of alcohol intoxication
  - D. 30-day Event Monitor
  - E. Both C & D
  - F. None of the ablove

Case study 2

- 45-year-old female with history of SVT with radiofrequency ablation several years ago & has been maintaining SR with Dofetilide 250 mcg BID and metoprolol succinate 25 mg daily. No other medications. She presents with a symptoms of a sinus infection. She was given a 5-day azithromycin (Z-pack) regimen. The first round was unsuccessful to clear infection, so a second round was ordered. During the second round, she experienced signs and symptoms of a yeast infection, and self treated with an OTC PO antifungal that is a CYP3A4 inhibitor. She experienced several syncopal episodes and presented to ED and found to have prolonged QTc per 12 lead EKG

Fitzgerald 2020

Question 2

- Patient is referred to PCP from ED. What would you do?

a) Discontinue the Dofetilide?
b) Educate patient of long QTc?
c) Refer patient for ICD implantation?
d) Increase metoprolol?
e) Not enough information?

Case study 3

- 66-year-old male has a history of HFrEF with LVEF 35%, biventricular ICD, persistent afib, STEMI, COPD, obesity, T2DM on insulin, HTN, CKD 3b, sedentary lifestyle. Medications: amiodarone 200 mg daily, metoprolol succinate 100 mg daily, Entresto 49-51 mg BID, spironolactone 25 mg daily, furosemide 40 mg BID, metformin 500 mg BID, Jardiance 10 mg daily, albuterol inhaler.
- Vital signs: HR 60 bpm, BP 90/52 mmHg, RR 22, Weight 276 lb, BMI 42
- Annual labs: TSH 12.9. c/o fatigue, decrease exercise tolerance, weight gain

Question 3

- You
  - A. Discontinue the amiodarone
  - B. Order a Free T4
  - C. Order levothyroxine
  - D. Both B & C
  - E. All the above
  - F. None of the above

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