Arrhythmia

INTRODUCTION

Arrhythmia, otherwise termed "irregular heartbeat or dysrhythmia" is the overarching term for a group of conditions where the heartbeat is irregular, too slow, or too fast. Abnormalities in the heart's natural pacemaker (the SA node) lead to inconsistent electrical impulses resulting in abnormal cardiac action potential. The most common cause of arrythmias is myocardial ischemia. Many other conditions may lead to abnormal cardiac action potential (see risk factors below).

Arrythmias are broadly classified based on location. Supraventricular tachycardia (SVT) originate at or above the atrioventricular (AV) node and is defined by a narrow complex. Supraventricular arrythmias include sinus tachycardia, atrial flutter, atrial fibrillation, supraventricular re-entrant tachycardias and focal atrial tachycardias.

Ventricular arrhythmias originate below the atrioventricular node, on the ventricular level. Ventricular arrythmias include premature ventricular beats or contractions, ventricular tachycardia, ventricular fibrillation and Torsade de pointes tachycardia.

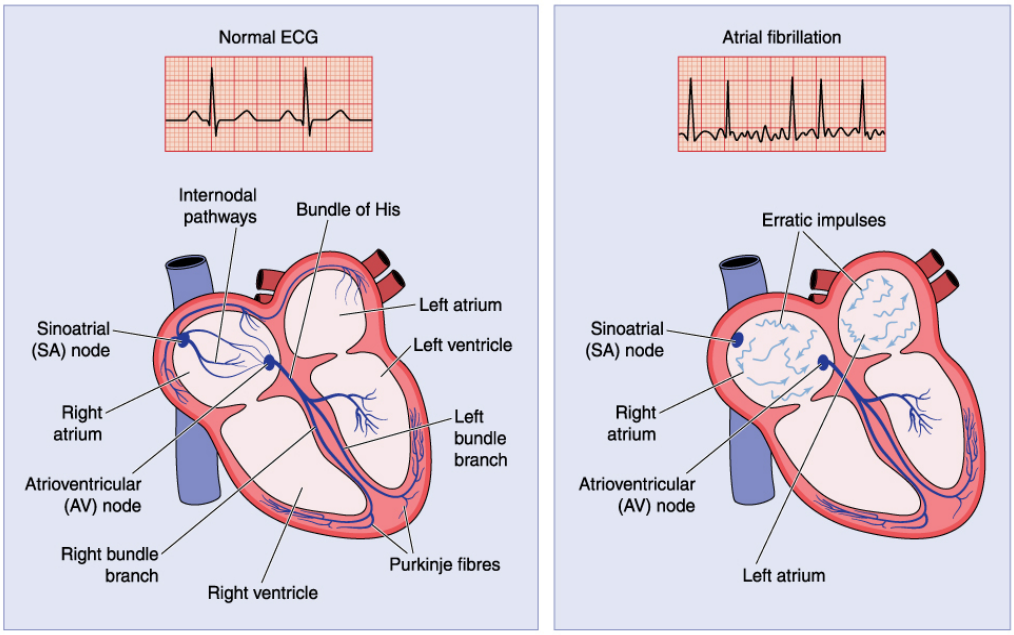
THERAPY GOALS
(supraventricular tachycardia)

- Restore normal sinus rhythm (this may not be possible in permanent AFib)
- Control rate in patients where rhythm may not be possible to control
- Prevent future events of arrythmia and reduce the risk of potentially fatal thromboembolic events

THERAPY GOALS
(ventricular tachycardia)

- Provide symptomatic relief
- Preventing fatal events

This chapter will predominantly review atrial fibrillation.



RISK FACTORS

- Medical conditions
  - Myocardial ischemia / Infarction
  - Underlying cardiac damage
  - Hypertension
  - Heart failure
  - Hyperthyroidism
  - Diabetes / sleep apnea
- Advanced age
- Electrolyte imbalances
- Medications that increase QT interval

CLINICAL PRESENTATION

- Asymptomatic
- Fatigue
- Chest pain
- Dizziness
- Palpitations
- Shortness of breath
- Syncope
- Bradycardia
- Tachycardia
- Irregular heart beats

Table 1: AFib classification

Type of AFib.	Description
Paroxysmal	Termination with or without intervention within 7 days
Persistent	Continuous AFib that lasts greater than 7 days
Long standing persistent	Continuous AFib that lasts greater than 12 months
Permanent	Joint decision by patient and clinician to stop trying to restore the normal sinus rhythm

MEDICATIONS THAT INCREASE QT INTERVAL

- Antiarrhythmics
  - Class I and III (mostly Ia)
- Antibiotics
  - Macrolides / quinolones
- Antidepressants
  - Mirtazapine, TCAs (amitriptyline, nortriptyline), SSRIs (citalopram; choose sertraline for cardiac patients), SNRIs, trazadone, bupropion,
- Antipsychotics
  - Haloperidol, olanzapine, ziprasidone, clozapine
- Anticonvulsants
- Antifungal
  - Itraconazole / ketoconazole
- Antiviral
  - Atazanavir, ritonavir, indinavir
- Ondansetron / donepezil
- Methadone / tramadol
- Verapamil / theophylline
- Solifenacin, tacrolimus, atomoxetine, alfuzosin, apomorphine

Risk factors for developing **Torsades de Pointes** include medications that cause QT prolongation, females, hypokalemia, hypomagnesemia, hear failure, digoxin use and bradycardia.

PharmaEpass

Type of SUPRAVENTRICULAR arrythmias
EKG: narrow QRS

Atrial Fibrillation / Atrial Flutter

Hemodynamically Stable

Rate control *see below

- AF ≥ 48 hours
  - Give warfarin for 3 weeks (until INR is 2-3)
  - CARDIOVERSION
    1. Electrical is preferred
    2. Antiarrhythmic
  - Oral anticoagulants for 4 weeks *stroke prevention see below
- AF < 48 hours
  - CARDIOVERSION
    1. Electrical is preferred
    2. Antiarrhythmic
  - Chronic Ventricular **Rate Control** ***see below**

Heart Failure
Beta blockers
+/- digoxin

No HF or CAD:
1. Beta blockers
2. Non-DHP CCB
3. Digoxin (if sedentary)

CAD:
1. Beta blockers (preferred)
2. Non-DHP CCB

Chronic Anti-arrhythmic Control (see rhythm control below)
(symptomatic with frequent episodes despite rate control therapy)

Heart Failure
Amiodarone is the drug of choice

No HF or CAD:
1. Propafenone
2. Flecainide
3. Sotalol

CAD:
1. Sotalol *avoid in elderly women
2. Amiodarone

If above measures fail use amiodarone if not being used already as the 1st line option

SUPRAVENTRICULAR TACHYCARDIA
EKG: lose p waves, 150-250 bpm

Give ADENISONE
- IV over 1-2 seconds
- Repeat in 1-2 mins if no response
- Repeat again for a total of 3 times

Verapamil/diltiazem or beta blockers administered if unable to give adenosine

Does rhythm convert? *EKG flatlines

If normal cardiac function:
1. Beta-blockers
2. Non-DHP CCB
3. Digoxin

If ineffective:
Use IV: amiodarone or procainamide

If EF < 40%:
1. IV diltiazem
2. IV amiodarone
3. Digoxin

Treat contributing factors
- Hypovolemia / Hypoxia
- Abnormal potassium levels
- Hypoglycemia
- Hypothermia
- Acidosis

Table 2: Rate vs. Rhythm Control

Management	Description

Rate Control
 	
Note that patients with atrial flutter may be more difficult to control than in those with atrial fibrillation.
	Pharmacological medications aim to lower heart rate to under 80 beats/minute
	• B-Blockers are preferred (metoprolol, atenolol, bisoprolol)
	  ○ Avoided in patients with asthma or if over 60 years of age
	• Calcium channel blockers (diltiazem, verapamil) are alternatives
	  ○ Avoided in patients with heart failure with reduced ejection fraction
	• Digoxin: blocks AV node and forces contractions
	  ○ Used in those who need immediate control with sedentary lifestyle
	  ○ Digoxin overdose: N/V, dreams, change in color perception

Rhythm Control	Generally,
	➢ If abnormal left ventricular function: use amiodarone
	➢ If normal ventricular function: use dronedarone, sotalol, propafenone or flecainide before moving onto amiodarone due to the limitation of side effects associated with amiodarone. See information on other drugs in the drug chart below.
	
	AMIODARONE (Class III antiarrhythmic):
	➢ Mechanism: block potassium channel
	➢ Amiodarone (class III antiarrhythmic) is the most effective antiarrhythmic but is associated with many side effects limiting its use → 2nd line option *see algorithm 1 for place in therapy
	➢ Useful in those with structural heart defects/heart disease
	➢ **Side effects**: hypotension, dizziness, ataxia, nausea, vomiting, constipation, tremors, skin photosensitivity, drug-induced lupus, bradycardia, insomnia and corneal microdeposits
	➢ Warnings:
	  ○ Photosensitivity (slate-coloured, blue-grey or purple discolouration)
	  ○ Severe skin reactions (SJS)
	  ○ Neurotoxicity
	  ○ Hyperthyroidism & hypothyroidism (inhibition of peripheral T4 to T3 conversion) *hypothyroidism is more common
	  ○ Retinal toxicity
	  ○ Avoid grapefruit juice while taking oral amiodarone
	➢ Monitoring
	  ○ Electrolytes, BP, HR
	  ○ Thyroid function / Transaminases (every 6 months)
	  ○ Pulmonary function
	  ○ Chest X-ray (annually)
	  ○ Ocular examinations
	➢ Interactions
	  ○ When initiating amiodarone – doses of warfarin, beta blockers and digoxin often require reductions by ½
	  ○ Substrate of CYP3A4, 2C8 and P-glycoprotein

ASSESSMENT OF ADJACENT TREATMENT

Risk of stroke assessment in patients with Atrial Fibrillation using:

CHADS2 score

C	Congestive heart failure	1 point
H	Hypertension	1 point
A	Age over 75	1 point
D	Diabetes	1 point
S	Stroke history	2 point

- If score is 1 or higher, oral anticoagulation initiated

Estimating bleeding risk in patients with Atrial Fibrillation using:

HAS-BLED

H	Hypertension	1 point
A	Abnormal kidney or liver function	1 point
S	Stroke	1 point
B	Bleeding	1 point
L	Labile INR	1 point
E	Elderly (over 65)	1 point
D	Drugs / alcohol use	1 point

***Post ACS*:**

If no PCI → Oral anti-coagulant (OAC) + clopidogrel x 12 months
then OAC alone x 12 months

If PCI → Triple Therapy (OAC + clopidogrel + ASA) x 6 months
then OAC + clopidogrel x 12 months
then OAC alone x 12 months

Prior GI bleed: Resume oral anti-coagulant

Low GFR: GFR 15-30: DOAC is contraindicated, use WARFARIN

Table 3: **Anticoagulant Comparison Warfarin vs. Novel Oral Anticoagulants**

Medication		Advantages & Disadvantages	Dose adjustment
DOAC	Apixaban	**Advantages**: • Works quickly - quick onset of action • Fixed dosing • Minimal drug / food interactions • **No need for monitoring - predictable** • Do need regular follow-up of levels • Reversal agent is available for dabigatran: Idarucizumab **Disadvantages**: • If a dose is missed, effect is decreased • Need to dose adjust in renal failure • Reversal agent is NOT available for apixaban, edoxaban, and rivaroxaban • Expensive compared to warfarin	SCr <133 and <60kg or >80 years Avoid if CrCl <15 mL/min
	Dabigatran		Increased risk of bleeding or >80y Avoid if CrCl <30mL/min
	Edoxaban		<60kg Avoid if CrCl <30mL/min
	Rivaroxaban		Avoid if CrCl <30mL/min

Warfarin	**Advantages**: • Cheap • Reversal agent is available • If a dose is missed, OK - lasts long time in the body **Disadvantages**: • Regular follow-ups needed • Need to monitor INR levels • May need frequent dose changes • Many drug interactions • Many food interactions • Timing of anticoagulation interruption: - Stop warfarin 5 days before surgery - Check INR 1 day before surgery • If INR is > 1.5, give patient 1 to 2 mg of vitamin K (PO)	Primarily metabolized by CYP450 enzyme system Monitoring: • Daily or every other day x 3 days • Every 3 days x 1 week • 1-2 x/week • Once stable every 2-4 weeks • If very stable, then every 12 weeks

INR Management **(TARGET INR IS 2.0 – 3.0)**

- INR < 1.5 → increase weekly dose by 10-20% *administered a 1-time dose of 20% of weekly dose
- INR between 1.5 and therapeutic range → 2 consecutive low readings → increase weekly dose by 10-20%
- INR < 5 but above therapeutic range → discontinue 1 dose OR reduce weekly dose by 10-20% once INR back within range
- INR 5-9 → discontinue 1-2 doses then recheck INR – continue therapy at 10-20% lower than weekly dose once INR back within range *Vitamin K 1-2mg is considered in patients at high risk of bleeding
- INR > 9 BUT no bleeding → discontinue (may administer vitamin K 2-5mg then recheck INR) and restart therapy at 20% lower than weekly dose once INR back within range

Table 4: DOACs trial recommendation

DOACs Trial Information		
Study name	**Drugs of study**	**Results**
ARISTOTLE	Apixaban vs Warfarin	Apixaban decrease stroke/systemic embolism, decreased ICH, major bleeds + similar GI bleeding
AVERROES	Apixaban vs ASA	Apixaban decreased stroke/systemic embolism + similar bleeding
RELY-AF	Dabigatran vs Warfarin	Dabigatran decreased stroke/systemic embolism but, increased GI bleeding; 110 mg dose had similar stroke/systemic embolism
ENGAGE-AF	Edoxaban vs Warfarin	Edoxaban decreased stroke/systemic embolism but, increased GI bleeding: 30 mg had similar stroke/systemic embolism
ROCKET-AF	Rivaroxaban vs Warfarin	Rivaroxaban similar stroke/systemic embolism + increased GI bleeding
Overall recommendation:	Use DOACs over warfarin unless the patient is on warfarin and is stable for non-valvular atrial fibrillation/ flutter. DOACs over warfarin for the treatment of VTE.	

Anticoagulation BEFORE and AFTER surgery

What are the indications for anticoagulation use?

- Mechanical heart valves
- Atrial Fibrillation
- Venous thromboembolism

What is heparin bridging?

- Patients cannot take warfarin before surgery. Heparin bridging covers the period before surgery to lower the risk of pre-surgery thromboembolism. It is used in patients with moderate to high thromboembolic risk. It can be done before surgery, after surgery, or both in some cases.

What agents are used instead of warfarin during this time?

- Short acting anticoagulants such as low molecular weight heparins (LMWH) or unfractionated heparin (UFH) is used.

When is LMWH/UFH started?

- Warfarin is stopped 5 days before surgery.
- LMWH or UFH is started 3 days before surgery when the INR is below the therapeutic range.

When is LMWH/UFH stopped?

- UFH should be stopped 4 to 6 hours before surgery.
- If LMWH was given BID: Stop the night before surgery.
- If LMWH was given once daily: Give 50% of the dose the morning before surgery. Do not give dose the day of surgery.

When to restart regular anticoagulation?

- Anticoagulation is started based on the patients bleed risk, hemostasis, and class of anticoagulation used.
- If the patient is using DOAC: can restart medicine day after surgery (moderate bleed risk).
- If the patient is using DOAC: can restart medicine 2 or 3 days after surgery (high bleed risk).
- If the patient is using warfarin: can restart warfarin the night after surgery if patient is drinking.

Patients high risk of pre-surgery thromboembolism?

Mechanical heart valve patients with:

- Mitral valve
- Recent stroke (within last 6 months)
- Recent TIA (within last 6 months)

Atrial fibrillation patients with:

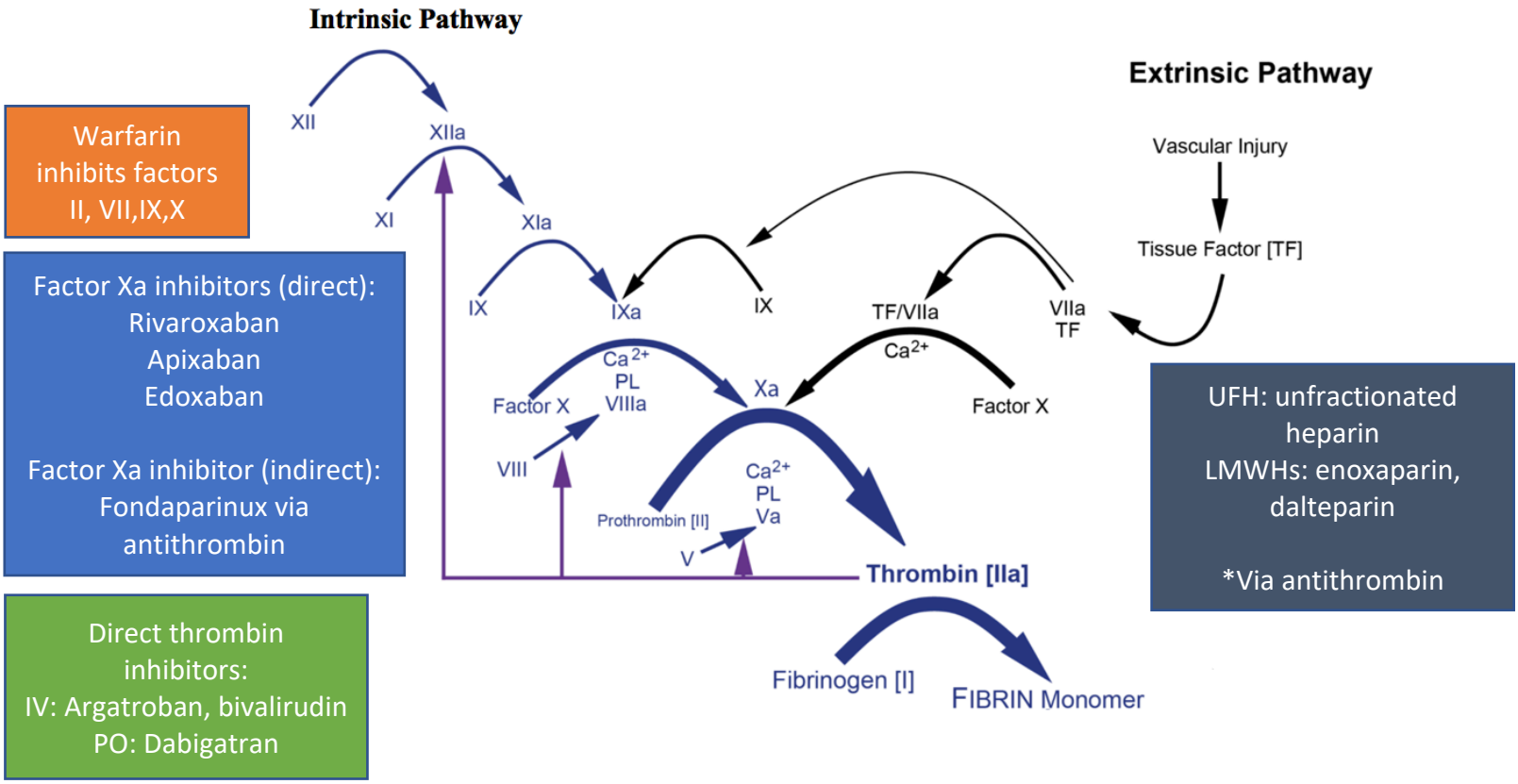
- CHADS2 score of 5 or more
- recent stroke (within last 3 months)
- recent TIA (within last 3 months)
- rheumatic valvular heart disease

Venous thromboembolism patients with:

- Recent VTE (within last 3 months)
- Severe thrombophilia (deficiency of protein C, S, antithrombin)

Pathway Mechanisms

The illustration below shows the coagulation cascade and drug location.



Choice of Antithrombotic Agent in Atrial Fibrillation

- Age 65 or older
- CHF
- Diabetes
- Previous Stroke/ TIA
- Hypertension
    - If YES to any, start on OAC **(DOAC > Warfarin) for Non-Valvular AFib**
    - If NO to these, consider presence of Coronary Artery Disease
    - If CAD, start on ASA
    - If NO CAD, does not need an anticoagulant at this time

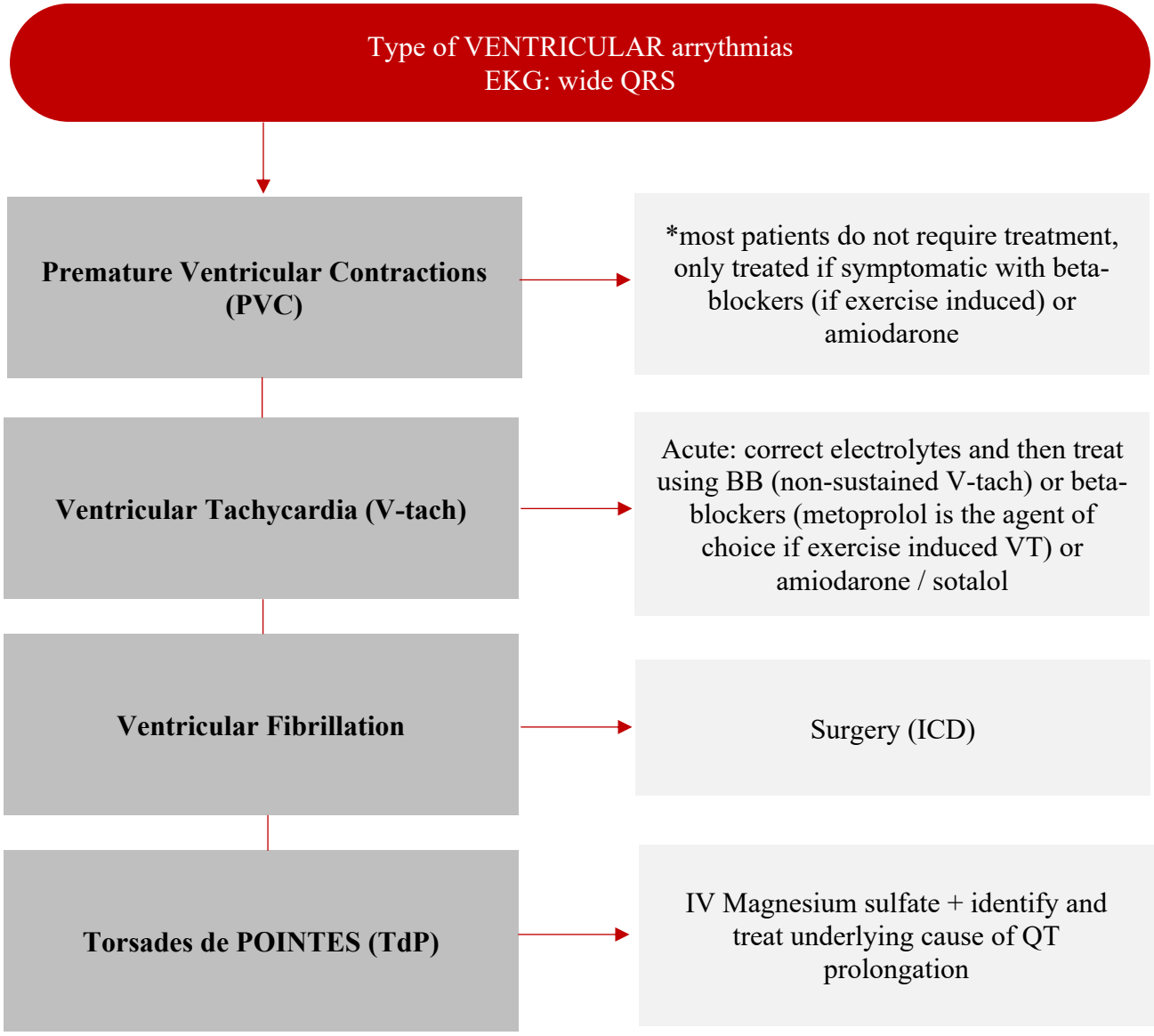


Table 5: antiarrhythmic drugs

Drug Class & Agent	Important Information
Class I (negative inotrope) **Mechanism**: sodium channel blockers	
Disopyramide Class IA	**Side effects**: dry mouth, constipation, hypotension, headaches and nausea **Used with caution** in patients with BPH, urinary retention and glaucoma **Interaction**: major substrate of CYP34A
Quinidine Class IA	**Side effects**: diarrhea, stomach cramps, nausea, vomiting, hearing loss, blurry vision and delirium.

Taken with food to reduce GI side effects *Blocks sodium and potassium channels*	Used with caution due to potential hepatotoxicity and drug induced lupus **Interactions**: ay cause digoxin concentration to rise - need to reduce digoxin dose by 50% if used together, inhibits CYP2D6 and Pgp - Avoid fluctuations in daily sodium intake
Procainamide Class IA	**Side effects**: hypotension, rash (with long term use) and may cause SLE (caution) **Interactions**: substrate of CYP2D6, amiodarone may elevate levels of procainamide
Mexiletine / lidocaine Class IB	Mexiletine: various CNS related side effect profile
Flecainide Class IC	**Side effects**: nausea, headache, tremor, burry vision, and dyspnea Interactions: major substrate of CYP2D6, avoid concurrent use with ritonavir
Propafenone Class IC	**Side effects**: nausea, vomiting, taste disturbance (metallic taste), constipation and headaches **Interactions**: major substrate of CYP2D6
Class II **Mechanism**: beta-blockers	
Class III **Mechanism**: potassium channel blockers	
Amiodarone	See rate control notes above
Dronedarone	**Side effects**: dyspepsia, nausea, vomiting, diarrhea, QT prolongation and increase in creatinine concentrations **Contraindication**: severe heart failure (NYHA class IV) **Interactions**: inhibitor of CYP34A, 2D6 and Pgp and avoid use with strong inhibitors / inducers of CYP3A4 (azoles / macrolides)
Sotalol (non-selective beta blocker)	**Side effects**: torsades de pointes, chest pain, fatigue, bradycardia, bronchoconstriction, vivid dreams, dyspnea, palpitations and wheezing Dosage adjustment required in patients with renal impairment
Ibutilide	Only given via IV in a hospital **Side effects**: hypotension and torsades de pointes.
Class IV **Mechanism**: Calcium channel blockers (non-dihydropyridines)	
Diltiazem Verapamil	**Side effects**: edema, dizziness, constipation (most common with verapamil), hypotension and gingival hyperplasia **Contraindications**: patients with severe hypotension or cardiogenic shock potential, postmyocardial infarction patients with ejection fraction <40%, second- or third-degree AV block, Wolff-Parkinson-White syndrome with AFib

	Avoid concurrent use with ivabradine
Cardiac Glycoside **Mechanism**: block Na-K-ATPase pump	
Digoxin	**Side effects**: headache, visual impairment, nausea, vomiting, diarrhea and dizziness **Contraindications**: ventricular fibrillation **Monitoring**: renal function, electrolytes, BP, HR, ECG • Disturbance in electrolytes (hypokalemia, hyperkalemia and hypomagnesemia increase the risk of toxicity) • Hypothyroidism may increase digoxin concentrations **Interactions**: when used alongside CCBs, BBs, amiodarone, propafenone or quinidine the dose of digoxin should be reduced by ¼ • Negative chronotropic (reduces heart rate) and positive inotrope (increases contraction force) **Toxicity** • Early: nausea, vomiting, loss of appetite, confusion and abdominal pain • Severe: visual effects (blurred vision, colour disturbances, haloes and scotomas), confusion and hyperkalemia