1 CLASS III — K^+ Channel Blockers (Prolongers of the AP, Refractory period)

- All Class I and III drugs are dose dependant (=higher efficacy during ↑ Excitability)

AMIODARONE

Mechanism:

- **Primary:** Blocks multiple **K^+ channels (IKr, IKs, IKur, IK1, KATP)** → markedly **prolongs AP duration + QT interval.** Pharmacology ML3 2.pdf
- **Secondary:** Blocks **inactivated Na^+ channels, Ca^{2+} channels, α & β receptors** → has Class I, II, III, IV actions simultaneously. Pharmacology ML3 2.pdf
  - ↳ Vehicles effect

Consequences:

- Slows HR & AV conduction. = Contraindicated in patients with Nodal diseases or AV Blocks
- Very **low TdP risk** despite QT prolongation. Effect on QT Adorgation and TdP?

Cardiovascular effect:

- Causes **peripheral vasodilation**, especially IV → acute **hypotension**. Pharmacology ML3 2.pdf
  - ↳ Through the α-Blocking effect of its Vehicle

Major Adverse Effects (HIGH-YIELD):

1. **Bradycardia / AV block** → contraindicated in nodal disease. Pharmacology ML3 2.pdf
2. **Extreme tissue accumulation** → huge Vd → **very long half-life**. Effects remain **1–3 months after stopping**. Pharmacology ML3 2.pdf
3. **Pulmonary fibrosis** (most dangerous) → fatal crisis. Pharmacology ML3 2.pdf
4. **Hepatotoxicity** – ↑ LFTs, cholestatic hepatitis → monitor LFTs. Pharmacology ML3 2.pdf
5. **Skin:** Photodermatitis + blue-gray discoloration. Pharmacology ML3 2.pdf
6. **Eye:** Corneal microdeposits, halos, optic neuritis → rare blindness. Pharmacology ML3 2.pdf
7. **Thyroid dysfunction** (contains iodine):
   - Blocks T4 → T3 conversion.
   - Can cause **both hypo- & hyperthyroidism** (Type 1 & Type 2).
   - Type 1 → treat with thionamides.
   - Type 2 → treat with steroids (prednisolone). Pharmacology ML3 2.pdf

- Lungs
- Liver
- Skin
- Eyes
- Thyroid gland

Pharmacokinetics:

- Bioavailability 35–65%.
- Metabolized by **CYP3A4** → huge drug interactions. (Rifampin (a CYP3A4 inducer) → ↓ Bioavailability of Amiodarone
- **Inhibits CYPs → ↑ levels of warfarin, digoxin, statins** → warfarin dose must be reduced 33–50%. Pharmacology ML3 2.pdf

Why it's widely used:

- A biphasic elimination:
  - Rapid phase: 3–10 days while drug is still mostly in plasma
  - Slow phase: several weeks once tissue stores dominate (average terminal half-life ≈ 50 days)

- Broadest spectrum antiarrhythmic & effective for most arrhythmias. Pharmacology ML3 2.pdf

- **Dronedarone, an analog that lacks iodine atoms, used for the treatment of atrial flutter and fibrillation.** (Not studied for V-Fib yet)

L-Form → β-blocking
L+D → AP prolongation

SOTALOL

Mechanism:

- Non-selective **β-blocker** AND **IKr blocker** → prolongs AP duration + ERP. Pharmacology ML3 2.pdf
  ↳only rectifier channel Blocker

Risks:

- **Dose-dependent Torsades de Pointes.** Pharmacology ML3 2.pdf
- Can worsen LV function → avoid in overt HF except evidence-based β-blockers.

Uses:

1. Life-threatening ventricular arrhythmias
2. **Maintenance of sinus rhythm** in AF (NOT conversion)
   = Arrhythmias + Maintainance of Sinus Rythm
3. Supraventricular + ventricular arrhythmias in pediatrics (amiodarone alternative). Pharmacology ML3 2.pdf

DOFETILIDE

Mechanism:

- **Pure IKr blocker** (dose-dependent).

PK:

- **100% bioavailable**.
- Eliminated renally → adjust dose by **Creatinine Clearance**.
- Verapamil ↑ plasma levels by ↑ intestinal blood flow.
- Renal cation secretion inhibitors prolong its half-life. Pharmacology ML3 2.pdf

Safety Requirements:

- Initiation must be **in hospital** with baseline QTc, K^+, Mg^{2+}.
- QTc ≥ 500 ms → reduce dose or discontinue.
- Contraindications:
  - QTc > 450 ms
  - Bradycardia < 50 bpm
  - Hypokalemia (must correct first) Pharmacology ML3 2.pdf

Main Indication:

- **Restoration & maintenance** of sinus rhythm in AF. Pharmacology ML3 2.pdf

2️⃣ CLASS IV — Ca^{2+} Channel Blockers (Non-DHP)

VERAPAMIL (± Diltiazem)

Mechanism:

- Blocks **L-type Ca^{2+} channels** in cardiac muscle + SA/AV nodes → ↓ HR (chronotropy), ↓ conduction (dromotropy), ↓ contractility.
  Mainly
- More cardio-selective (less vasodilation) than diltiazem → preferred in arrhythmias. Pharmacology ML3 2.pdf

Effects:

- Slows SA node firing
- Strongly prolongs **AV nodal conduction time + refractory period**
- Suppresses early & delayed afterdepolarizations. Pharmacology ML3 2.pdf

Dangers:

- Giving to **misdiagnosed VT with narrow QRS** → can cause **severe hypotension + VF**. HIGH-YIELD. Pharmacology ML3 2.pdf
  Diagnosed as a SVT due to its Narrow QRS
  → Due to the Vasodilatory effect of Verapamil
- Contra in AV nodal disease → may cause AV block (treat with atropine or β-agonists). Pharmacology ML3 2.pdf
- Constipation, peripheral edema.

Uses:

1. **Supraventricular tachycardia (SVT)**
   Ventricular
2. **Rate control** in AF/flutter (but does NOT convert rhythm).
   - Works by slowing conduction through AV node only (does not affect atrial re-entry circuits). Pharmacology ML3 2.pdf

Important Warning:

- **Do NOT combine: Verapamil + β-blocker + digoxin**
  → severe bradycardia, hypotension, AV block. Pharmacology ML3 2.pdf

3️⃣ OTHER ANTIARRHYTHMIC AGENTS

ADENOSINE

Mechanism:

- Natural nucleoside
- Activates **K^+ efflux** → hyperpolarization
- Reduces Ca^{2+} influx → suppresses Ca^{2+}-dependent APs
- Strongly **blocks AV node** (increases refractory period). Pharmacology ML3 2.pdf

PK:

- Half-life **< 10 seconds** → given as IV infusion/rapid bolus.

Use:

- **Drug of choice** for **acute conversion of paroxysmal SVT**. Very high efficacy. Pharmacology ML3 2.pdf

Interactions:

- Less effective with **caffeine/theophylline** (receptor blockers).
- Stronger with **dipyridamole** (uptake inhibitor).

Adverse effects:

- Flushing (20%), chest burning, dyspnea → avoid in asthma. (Due to Vasodilation) → Most common
- Very short-lived AV block (Fades upon cessation)
- Hypotension, headache (Vasodilation)
- Side effects disappear in seconds due to ultra-short half-life. Pharmacology ML3 2.pdf

IVABRADINE

Mechanism:

- **Selective blocker of If ("funny") current** in SA node.
- ↓ slope of phase 4 depolarization → **pure HR reduction**.
- No effect on contractility, repolarization, or conduction.
- **Use-dependent open-channel blocker**. Pharmacology ML3 2.pdf

Key Property:

- **Does NOT fully block If** → autonomic modulation (sympathetic/parasympathetic) is preserved.
  → Physiological HR responses remain intact. Pharmacology ML3 2.pdf

Uses:

- Antianginal, anti-ischemic
- CAD with high HR
- HF patients with HR > 70 when β-blockers inadequate
- Inappropriate sinus tachycardia Pharmacology ML3 2.pdf

Adverse:

- Visual brightness phenomena → due to If channel in retina. Pharmacology ML3 2.pdf

MAGNESIUM

Mechanism:

- Influences Na^+/K^+ ATPase, Na^+, K^+, and Ca^{2+} channels.
- Used especially for **digitalis-induced arrhythmias** or **torsades de pointes**.
- Works even if Mg^{2+} level is normal. Pharmacology ML3 2.pdf

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POTASSIUM — Clinical Effects

Hypokalemia (↓ K^+)

- ↑ K^+ efflux → hyperpolarization
- Hyperpolarization reactivates Na^+ channels → **↑ excitability**
- Causes **SVT, VT, TdP, ectopic beats**
- Very dangerous with digitalis. Pharmacology ML3 2.pdf

Hyperkalemia (↑ K^+)

(SA node Membrane Potential Stabilization → ↓ Rate of firing)

- ↓ K^+ efflux → partial depolarization → **↓ Na^+ channel availability**

↓
Used also to supress Ectopic Pacemakers

- Causes **bradycardia, AV block, wide QRS, asystole.** Pharmacology ML3 2.pdf

Key Rule:

- Always **normalize K^+** before giving antiarrhythmics. Pharmacology ML3 2.pdf

Drug / Class	Mechanism of Action	Main Clinical Uses	Major Adverse Effects / Dangers	Important Notes
Amiodarone (Class III, broad-spectrum)	Blocks multiple K^+ channels (IKr, IKs, IKur, IK1, KATP); also blocks Na^+, Ca^{2+}, α, β receptors → ↑ AP duration & QT	Most supraventricular & ventricular arrhythmias	Pulmonary fibrosis, thyroid dysfunction (↑ or ↓), blue-gray skin, photosensitivity, hepatotoxicity, corneal deposits, optic neuritis, bradycardia, AV block	Very long half-life (weeks–months), massive tissue accumulation, CYP3A4 interactions; ↑ digoxin/warfarin/statins; reduce warfarin dose 33–50%
Sotalol (Class III + β-blocker)	Non-selective β-blocker + IKr blockade → prolongs AP & ERP	VT, AF maintenance, SVT/VT in pediatrics	**Dose-dependent torsades de pointes**, worsened LV function	Not cardio-selective; alternative to amiodarone in young patients
Dofetilide (Pure Class III)	**Pure IKr blocker**; dose-dependent QT prolongation	Restoration + maintenance of sinus rhythm in AF	Torsades de pointes, severe QT prolongation	Must be started in hospital; avoid if QTc > 450–500 ms; avoid bradycardia < 50 bpm; correct K^+/Mg^{2+} first; renally eliminated → dose by CrCl
Verapamil (Class IV)	Blocks L-type Ca^{2+} channels → slows SA firing, slows AV conduction, ↓ contractility	SVT; control ventricular rate in AF/flutter	Hypotension, AV block, HF worsening, constipation, peripheral edema	DO NOT give in VT (can cause VF); avoid combination with β-blockers & digoxin (risk of severe bradycardia/AV block)
Diltiazem (Class IV)	Same as verapamil but less cardio-selective	Same as verapamil; rate control	Same as verapamil	Slightly more vasodilation than verapamil
Adenosine	↑ K^+ efflux; ↓ Ca^{2+} influx → strong AV nodal block; hyperpolarization	**Drug of choice for acute PSVT**	Flushing, dyspnea/bronchospasm, chest burning, very transient AV block, hypotension	Very short half-life (< 10 sec); less effective with caffeine/theophylline; potentiated by dipyridamole; avoid in asthma
Ivabradine	Selective **If (funny current) blocker** in SA node → ↓ HR (pure chronotropic effect)	Stable angina, CAD, HF with HR > 70, inappropriate sinus tachycardia	Visual brightness phenomena (phosphenes)	**Does NOT fully block If**, so autonomic regulation (SNS/PNS) still works → HR can still increase when needed
Magnesium	Modulates Na^+/K^+ ATPase, Na^+, K^+, and Ca^{2+} channels	Digitalis-induced arrhythmias; **torsades de pointes**		Works even if magnesium level is normal
Potassium (Clinical effect)	Changes resting membrane potential and excitability	Correction of hypo/hyperkalemia to prevent arrhythmias	Hypokalemia → SVT, VT, TdP; Hyperkalemia → bradycardia, AV block, wide QRS	ALWAYS correct K^+ abnormalities before giving antiarrhythmics