Arrhythmias are caused by defects in signal formation and/or conduction

ABNORMAL FORMATION

- Abnormal automaticity of SA/AV cells (altered rate)
- Abnormal automaticity of cardiac muscle cells (premature beats)

→ Defects in Automaticity

→ **DECREASE AUTOMATICITY**

1. Increase threshold potential
   - Class I: Na^+ channel blockers
     - IA - procainamide
     - IB - lidocaine
     - IC - flecainide, propafenone
2. Decrease phase 4 slope
   - Class II: β antagonists
     - Atenolol
     - Metoprolol
3. Increase AP duration
   - Class III: K^+ channel blockers
     - Amiodarone – has extra-cardiac toxicities
       - skin/mucosal discoloration
       - hypo/hyperthyroidism
       - hepatic/pulm toxicities
       - peripheral neuropathy
     - Dofelitide
     - Ibutilide
   - Class IA: Na^+ channel blockers
     - Procainamide – also K^+ channel blocker
4. Slow SA/AV node depolarization
   - Class IV: Ca^{2+} channel blockers
     - Diltiazem
     - Verapamil
       - only non-dihydropyridines
       - act on cardiac tissue AND vascular smooth muscle
5. Increase max diastolic potential
   - Other - nucleoside
     - Adenosine – promotes K^+ efflux

ABNORMAL CONDUCTION

- Reentry Rhythms
  1. tissue damage
  2. uni-directional block
  3. time for retrograde signal > refractory period
- AV blocks
  - Can't treat

→ Structural defects creating reentry circuits

→ **INCREASE ADP + RP**

→ **IA + III**

→ **DECREASE CONDUCTION VELOCITY**

Disrupt timing of reentry circuit

SA/AV (Ca^{2+} dependent depolarization) vs CM (Na^+ dependent depolarization)

AV blocking drugs "Nodal agents"

- Class II: β antagonists
  - Atenolol
  - Metoprolol
  - Slow Na^+ influx
  - reduce phase 4 slope
- Class IV: Ca^{2+} channel blockers
  - Diltiazem
  - Verapamil
  - Slow Ca^{2+} influx
- Adenosine – Inhibits Ca^{2+} channel opening

→ Slow Conduction through AV node

DIGOXIN slows aberrant depolarization wave reaching AV node.

- doesn't actually block AV node but prevents signal from reaching it.

Inhibits Na^+/K^+ ATPase

→ buildup of Na^+ in cell → more pumped out Na^+/Ca^{2+} exchanger

→ ↑Ca^{2+} entering cell

↑inotropy in treating HF and lengthens myocardial AP.

CM

- Class I: Na^+ channel blocker
  - Procainamide – mod.
  - Lidocaine – weak
  - Flecainide, Propafenone – strong

Slow depolarization of non-nodal tissue and slow conduction velocity

- Class II: β blockers
  - Atenolol
  - Metoprolol

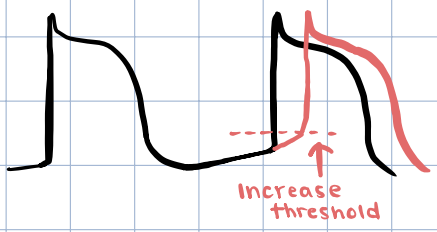
reduce sympathetic stimulation of CM depolarization → ↓conduction velocity

- Class IV: Ca^{2+} Channel blockers
  - Diltiazem
  - Verapamil

Slow Ca^{2+} dependent phase 2 depolarization of CMs → ↓conduction velocity

DECREASE AUTOMATICITY

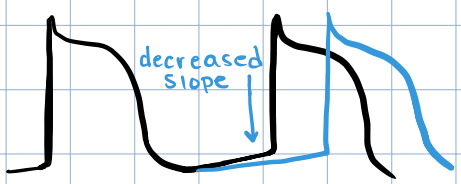
① Increase depolarization threshold



Block Na^+ channels → increased threshold

- Delays second beat by slowing the resetting of Na^+ channels after an AP.
- By binding open/inactive states, they are selective for rapidly depolarizing tissues

② Decrease phase 4 slope



Block B_1 receptor → slows HR

- takes longer to reach threshold potential
- prevents arrhythmia and decreases blood pressure.

③ Increase action potential duration

Block K^+ channels → extend plateau and slow repolarization

Toxicities: prolonged AP → prolonged QT → Torsades

④ Slow depolarization in SA/AV node cells.

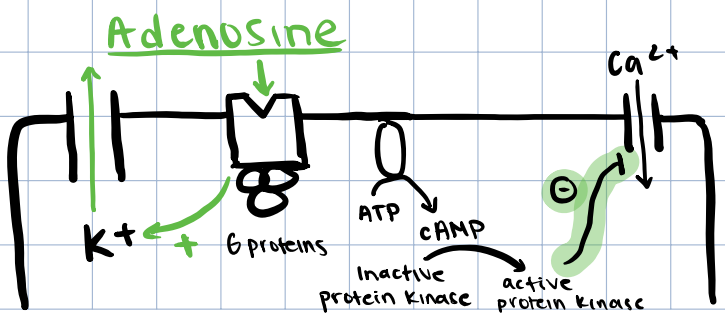
Ca^{2+} is responsible for rapid depolarization in SA/AV nodes.

Block Ca^{2+} channels → slows abnormal impulses

⑤ Increase maximum diastolic potential

Make the interior of the cell more negative between action potentials.

- hyperpolarize muscle cell by promoting K^+ efflux → increases diastolic membrane potential.



ATRIAL FIBRILLATION

irregular and erratic rhythm

Increases risk of clotting events.

- Atria beating irregularly → blood pools → clots in atria

Anti-Clotting Drugs - usually required in Afib patients

1. **Dabigatran**: factor IIa (thrombin) inhibitor.
2. **Apixaban**: factor 10 inhibitor
3. **Rivaroxaban**: factor 10 inhibitor
4. **Warfarin/Coumadin**: vitamin K inhibitor. Indirect-acting.

RATE vs. RHYTHEM CONTROL

Afib can produce ventricular tachycardia/fibrillation.

Rhythm Control: use of drugs to restore normal sinus rhythm.

Amiodarone restores NSR by interrupting the atrial reentry circuit by increasing myocyte refractory period (K^+ channel blockade)

Rate Control: use of drugs to slow ventricular rate in response to Afib

AV blocking drugs prevent signal from passing through AV node.

- β-antagonists (+amiodarone)
- Ca^{2+} channel blockers
- Adenosine - has β-blocking activity and can be AV blocking agent.
- Digoxin - slows aberrant depolarization wave reaching AV node

Treatment of Afib is complicated by:

drug-drug interactions

Amiodarone ⊣ CYP2C9

Warfarin → warfarin → Increased toxicities

Amiodarone also blocks excretion of digoxin.

concomitant conditions

HF	HTN	Afib
b blocker	b blocker	b blocker
ACEi	ACEi	Digoxin
Diuretic	Diuretic	Amiodarone
Digoxin		Non-DHP CCB
		Warfarin

Worsened by: b blocker + non-dhp CCB

b blockers worsen: diabetes, asthma, COPD