Antihyperlipidemic Drugs

1. **decrease production** of the lipoproteins **carriers** of cholesterol and triglyceride.

2. others **increase the degradation** of lipoproteins.

3. **decrease** cholesterol **absorption** or directly **increase** cholesterol **removal** from the body.

↓ LDL — statins

↓ VLDL — Fibrates

↑ HDL — Niacin

↑ removal — Bile acid-Binding resins

↓ Absorption — Cholesterole absorption inhibitors

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS (VLDL)
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑ as a feedback loop	↓↓
Fibrates	↓	↑↑↑	↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Statins

Contraindication ممنوع نعطيه ❌
- ↳ pregnancy
- ↳ children [relative contraindication for children > 8 years]
  familial hypercholesterolemia إذا كان عنده
  بهاي الحالة ممكن نعطيه

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

HMG CoA inhibitors

↓ concentration of cholesterol whithin hepatocytes (liver)

- ⊕ synthesis of **LDL** receptors
  - ↑↑ uptake of LDL (blood → liver)
  - **↓↓↓↓ LDL**
- ⊖ Secreation of **VLDL**
  - [from Liver ↛ blood]
  - **↓↓ VLDL**

⊕ **HDL** as a feedback loop

السبب ← ال HDL بجيب ال cholesterol
من ال Tissues ⟵ Liver
فهون لأن ال cholesterol ↓↓
فال **↑↑ HDL** مشان يعوض النقص

Statin at night before sleep يأخذ

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medium activity

- Lovastatin } → الأضعف
- fluva statin }
- Prava statin → مسموح مع ال fibrate ✱
- Simva statin

high efficacy & potancy & Emax

- عطر ● Atrovastatin
- rose = الورد ● rosuva statin

Aggressive Dose

✓ زيادة ال Dose حسب الحالة

⇒ Statin catabolism through

Cyp 3A4	**Cyp 2C9**	**Sulfunation**
نحب Lova	(rose) rosuva	Prava
أشمّ Simva	(flower) fluva	
العطر Atorva		

side effects

-Biochemical abnormalities in liver function (evaluate liver function is needed)

-Myopathy ⇒ inhibition of Co-enzyme q10 ⇒ ↓ATP

Amiodarone
Verapamil
grapefruit juice

تناول ال statin مع ↑ risk of myopathy

rhabdomyolysis (disintegration or dissolution of muscle). ⇒ ↑ Creatine Kinase [CK]

rare

إذا ما صار مراقبة (monitoring) وصل تركيز [CK] عالي كثير

ح يزيد myoglobulin ⇐ بترسب في ال Kidney ⇐ nephrotoxicity

Fibrates

فنين يلي بروح على الجيم المفروض ياكل Fiber بس هو أكل بيتزا

ردها

- Fenofibrate
- Gemfibrozil ⇒ high potancy
  Contraindicated with statin ممنوع
- Bezafibrate

Peroxisome proliferator activated receptors (PPARs) are a nuclear receptors that regulate lipid metabolism.

Fibrat triacylglyceroles **binding** to these receptors result in reduction of concentration by increasing the expression of lipoprotien lipase.

↓ Triglycerides ↓ VLDL

↑ entery of free fatty acids toward tissues

- They are used in the treatment of hypertriglycerolemias.

side effects

a. The most common adverse effects are mild gastrointestinal disturbances.

b. **Lithiasis**: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of **gallstones**. → ↓ production of Bile acid
↳ main componant more lipidic
↳ gallstones

d. **Myositis** (inflammation of a voluntary muscle) can occur.

إذا المريض أخذ Statin + Fibrate [التنين بصيرلهم Catabolism by Cyp450]
ح يزيد ال myopathy بس مش Contraindicated لبعض

Niacin (Vitamin B_3)

↓ LDL
↓ VLDL

↑HDL

Strongly **inhibits Lipolysis** in **Adipose** tissue

by ⊖ Hormonal Sensitive Lipase HSL

* **inhibits the uptake of HDL** toward liver (blood → liver) blood ضنزيد في ال

* **↓ Catabolism of HDL** by foam cells

Side effects

- Cutaneous flushing, burning and itching

السبب ⇒ ↑prostaglandin ⇒ ↑peripheral Dilation

Profen / Aspirin مشان فك هاي المشكلة بنعطي

- GI irritation, nausea and vomiting.
- Peptic ulcer activation
- elevation of liver enzymes

- hyperglycemia (↑ insulin resistance)
- hyperuricemia.

Niacin

من الأدوية يلي بنعطيها

Escalation

بعين بنعطي بالبداية dose قليل
وبنرفعه شوي شوي

Bile acid – Binding resins

- Cholestyramine
- Cholestipol

resins bind to Bile acid

↳ Forming insoluble complexes

↳ excreted in the feces

Lowering bile acid level will trigger the conversion of cholesterol into bile acid and the end result will be a reduction in the cholesterol concentrations.

↑ removal of cholesterol

[↓ cholesterol store]

يأخذ With Food

↓ LDL

minimal effect on VLDL

⊛ Bile acid – Binding resins

For patients who can Not Tolerate statins

or Combinate with statin

side effects

gastrointestinal disturbances such as **constipation** and **nausea**.

*

- At high doses they impair the absorption of **fat soluble vitamins (A,D,E, and K).** AKED

- These agents interact with the absorption of many drugs, for example, **Tetracycline, Digoxin, Warfarin, Aspirin.**

Cholesterol Absorption Inhibitors

Ezetimibe

يأخذ with food

selectively inhibit intestinal absorption of dietary and biliary **cholesterol** in the small intestine,

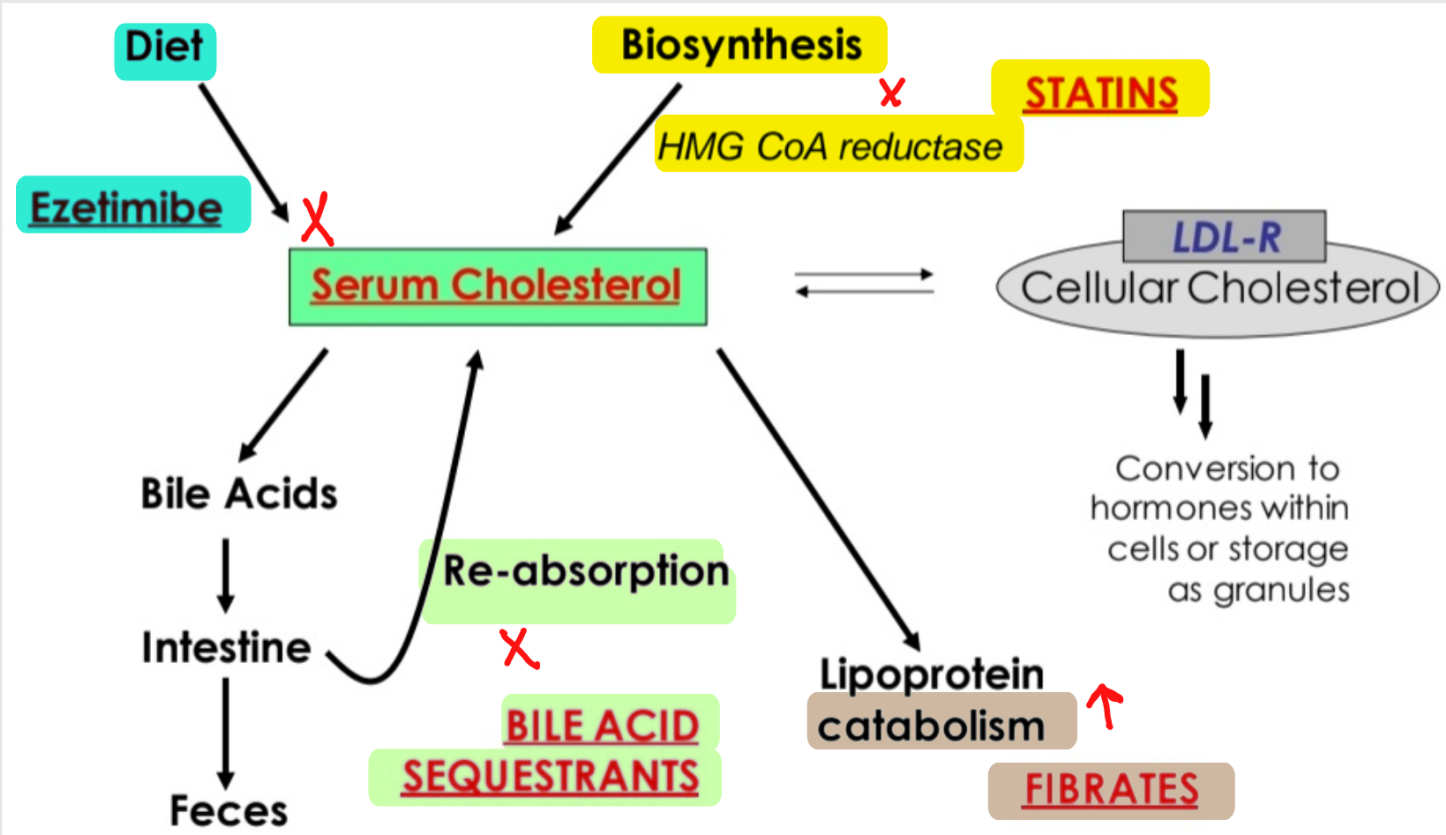
resulting in an **increase** in the clearance of cholesterol from the **blood**.

mild / Limited activity

- Good combiner with statin
  - Synergestic activity toward ↓ LDL

side effects

headache and/or **diarrhea**. *



If you know that Hyperlipoproteinemia Type IIa [familial hypercholesterolemia] will elevate LDL only , which is the drug of choice?

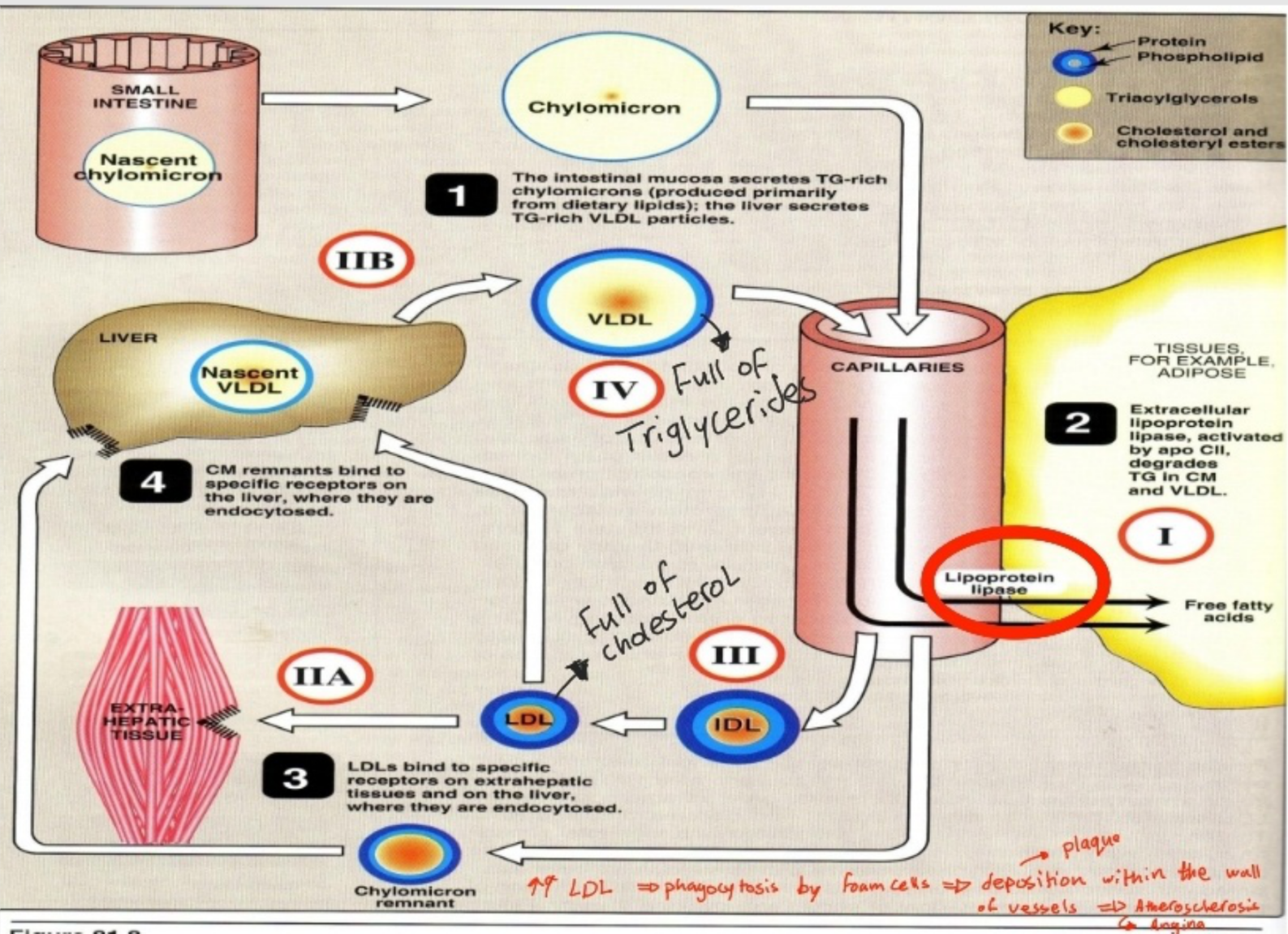
Statin OR Bile acid binding resins (in combination with dietor or Nacin)

If you know that Hyperlipoproteinemia Type IIb [Combined hyperlipidemia] will elevate LDL / VLDL /Triglycerides , which is the drug of choice?

Statin +Fibrate

If you know that Hyperlipoproteinemia Type IV [familial hyperlipidemia will elevate VLDL , which is the drug of choice?

Fibrate

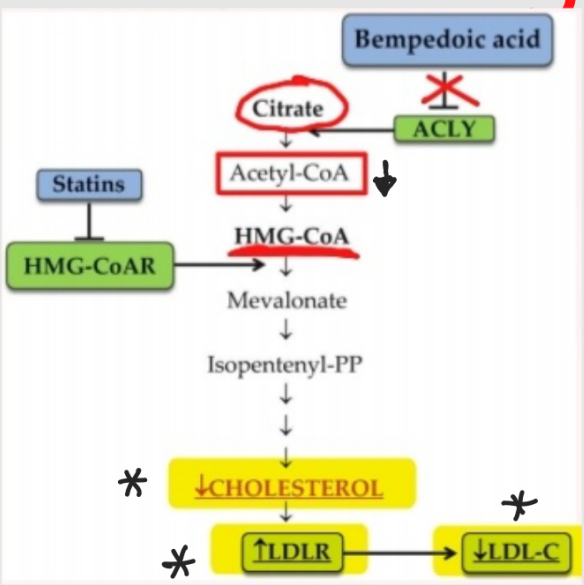


New Lipid Lowering Agents

- LDL-C Lowering Agents
  - Bempedoic acid
  - PCSK inhibitors
    - monoclonal antibodies
    - RNA silencing
- VLDL Lowering Agents
  - ApoC-III inhibitor
  - ANGPTL3 inhibitor

1 Bempedoic Acid

Selective antagonist of ACLY



ATP-citrate lyase (ACLY) catalyzes the ATP-dependent conversion of citrate and coenzyme A (CoA) to oxaloacetate and acetyl-CoA.

Acetyl-CoA, the precursor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), is crucial for the biosynthesis of cholesterol.

* Bempedoic Acid inhibits an Enzyme that is upstream to HMG-R

- **prodrug** and requires activation by very-long-chain acyl-CoA synthetase-1
- Combined with
  - Statin
  - Ezitimibe → to inhibit the increase of Absorption of cholesterol by GI tract (Deudenum)

side effects

increase of blood **urea nitrogen, creatinine,** and **uric acid.** → Gout

It also resulted in a **decrease** in **hemoglobin.** → Anemia

2 PCSK9 inhibitors

* may combine with statin

Proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme predominantly produced in the liver, binds to the LDL receptor (LDLR) present on the surface of the hepatocytes, leading to its degradation and a subsequent increase in plasma LDL-C levels

Thus, inhibition of PCSK9 causes an increase in LDLR number and a subsequent decrease in plasma LDL-C levels

By

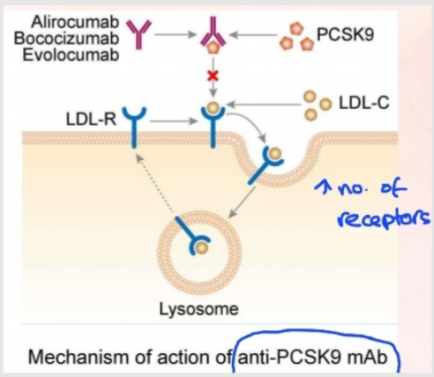
Monoclonal Antibodies

- evolocumab
- alirocumab

* No side effect

except

Flue-like Syndrome



Mechanism of action of anti-PCSK9 mAb

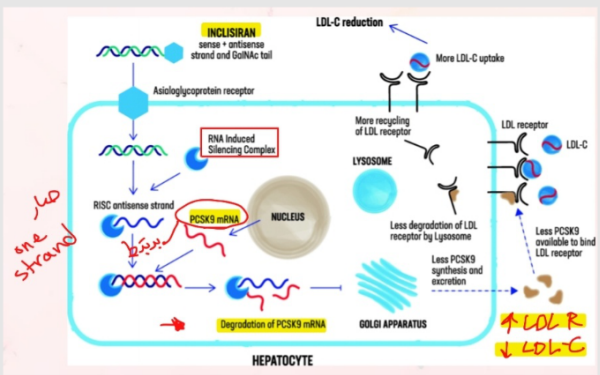
RNA Silencing

- Inclisiran

synthetic small interfering RNA (siRNA)

very expensive

* No side effect



Compliance ⊛ المرضى ماهي دواعي مخاوف من ال

Adherance of patient to the drug

Both have Loading Dose ⊛

كلاهما mAb بس ال

3 ApoC-III inhibitor

↓ VLDL
↓ Triglyceride
* ↓ Chylomicron

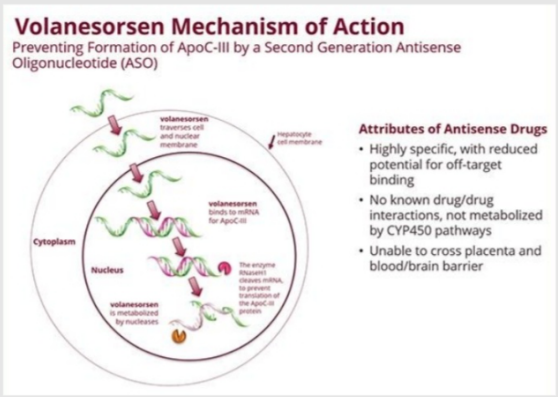
Apolipoprotein C-III (apoC3) is a key regulator of TG metabolism.
• It is a potent **inhibitor** of lipoprotein lipase (LPL), the enzyme responsible for the lipolysis of TG in the very-low-density lipoprotein (VLDL) and chylomicron particles.

Volanesorsen

Antisense Oligonucleotide ASO

targeting → ApoC-III mRNA

For patients with elevated plasma TG levels and in patients with familial chylomicronemia syndrome (FCS)



side effects

thrombocytopenia and injection-site reactions

common SE

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4 ANGPTL3 inhibitor

↓ TG
↓ VLDL

ANGPTL3 regulates plasma TG and HDL-C levels by inhibiting lipoprotein lipase (LPL) and endothelial lipase, respectively.

Inhibition of ANGPTL3 preserves the function of LPL and EL with a subsequent decline in TG, LDL-C and HDL-C plasma levels independently of LDLR function

Evinacumab

monoclonal antibody

Vupanorsen

antisense oligonucleotide
↳ siRNA

Influenza like effect

NO side effects

Antiarrhythmic Drugs

Class I

• Na+ channel blockers
(in phase 0)

myocyte بشتغل على ال

* بمنع دخول ال Na^+ ← phase 0
بمنع خروج ال K^+ ← phase 3

[*] يؤدي إلى
prolonged QT interval
وهاد خطير جداً!
لأنه بشتغل على ال Duration of Action potential & Refractory period

Class Ia

intermdiate (moderate)

Action potential
reduce AP conduction velocity
effective refractory period
increase ERP and APD duration

For Supraventricular Tachyarrhythmia [Atrial fibrillation]
& ventricular Tachycardia ← بشرط
ما بينعطى مع دوا بيعمل elongation QT-interval

* early depolarization
ال message يلي كانت تيجي ب phase3 قبل ال resting ع تعمل تأثير depolarization

quinidine, procainamide أحسن

S.E. Torsades de pointes with QT interval prolongation
* GIT side effects: diarrhea, nausea, vomiting
* Cinchonism: a syndrome of headache, dizziness and tinnitus → طنين الأذن
* May increase the plasma concentration of **digoxin** leading to digitalis **toxicity**

Class Ib

shortens both APD and ERP
يزيد frequency of Beats

* Ventricular tachyarrhythmias
prolongation of QT interval ✓
Contraindication in arrhythmia ← إلا بحالة واحدة

lidocaine

Class IC

marked Block
أكثر affinity ← يمنع دخول ال Na+ أطول
> 10 sec

Reduce AP conduction velocity
* Maintain normal ERP and APD
Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation);
• Ventricular tachyarrhythmias resistant to other treatment

Class II

• ca2+ channel blocker
(in phase 0)

increased [cAMP]i activates protein kinase A, which phosphorylates a wide range of ion channels

• reduce AV node conductivity

Class II a

Non selective & selective B-blockers
↳ β_1 – adrenergic R. inhibitor

Class II d

Muscarinic M2 receptor activators *

Digoxin

↳ AV node inhibition
For Sinus Tachy cardia
" Supraventricular "

S.E bradycardia
AV block
Ventricular Tachycardia

Class II e

Adenosine A1 receptor activators *

α, β] inhibitory activity of Ca^{++} entry to AVN/SAN
γ ⇒ activation of K^+ channels (hyperpolarization)
بدل ما يكون rest mp = -90 ← -110 بعيد عن ال threshold

Adenosine → بشتغل بسرعة، بنتهي بسرعة

إذا ما بدنا نعطي DC shock ✓
بصفر ال ECG ← For 30 sec

-ve chronotropic
↳ reduce automaticity of pace makers < SAN, AVN
-ve dromotropic (التوصيل)
↳ ⊝ AV-nodal conduction

For Acute termination of AVN Tachycardia

بالعادة، المشكلة في ال Atria بس ممكن أتدخل بال ventricles ← cAMP إذا كان بسبب

S.E → Sinus bradycardia, sinus arrest or AV block
Atrial fibrillation

Class III

• K+ channel blockers
(in phase 1)

resulting in prolonged atrial, Purkinje, and/or ventricular myocyte

increased ERP, and reduced repolarization

Side effects
Torsades de pointes with QT prolongation Heart failure.
• Heart block
• Bradycardia

amiodarone
nonselective
also Block Na^+ channel
* orally
* long term effect (سيئة)
* For ventricular OR Supra ventricular Tachycardia
except إذا كان شي QT-interval elongation
لا ما بنعطي هاد الدوا

sotalol Selective
also β_1- blocker
يعني إله تأثير على Ca^{++} channel
* Drug of choice in pediatric arrhythmia

Class IVa

• Ca2+ channel blockers
| L-Type |
(in phase 0)

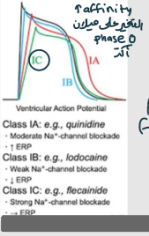
• reduce the conductivity & automoticity in AV node
بشتغل على ال AV node وليس ال myocite

For Atrial fibrillation or flatter

Supraventricular Tachycardia

Bepridil
Nonselective

verapamil
diltiazem
Selective



propafenone, flecainide

S.E

Ventricular tachycardia in presence of

Atrial Fibrillation

ischemic heart disease or old MI

but → Contraindication if there is

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* Torsades de pointes ??

→ No p.wave

→ message from everywhere in ventricle

early depolarization بسبب

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* class I , III ⇒ pro-arrhythmiac drugs

بيشتغلوا على ال myocyte

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* class Ia ⇒ elongation of QT بطول

class Ib ⇐ عكس

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* Digoxin + Adinosine

muscleanious Antiarrhythmic drugs

---

* class II , IV ⇒ For Atrial ....

Supraventricular ....

X entery of ca^{++}

* Ventricles ⇒ Na^{+} بتعمل على

بالبديهة بدي أطلش بالأدوية يلي بتشتغل على ال AV node

إذا حارز بجاج ال myocyte