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no.

CVS PHARMACOLOGY

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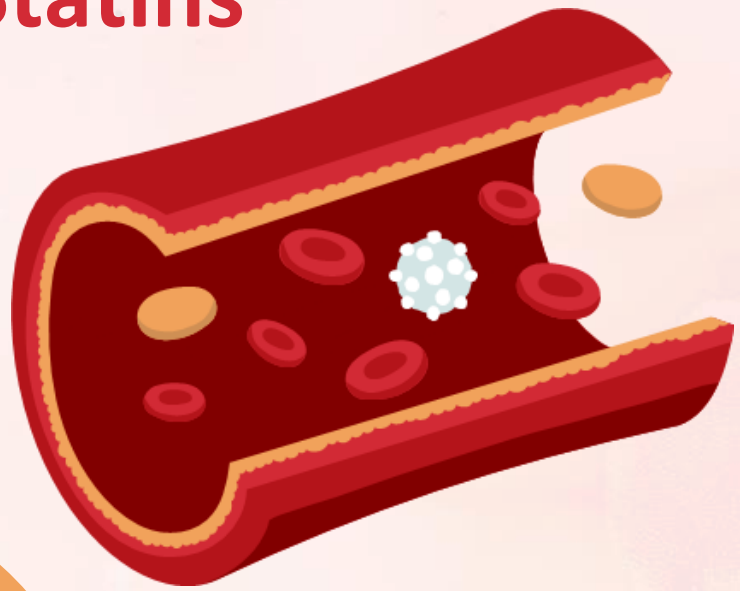
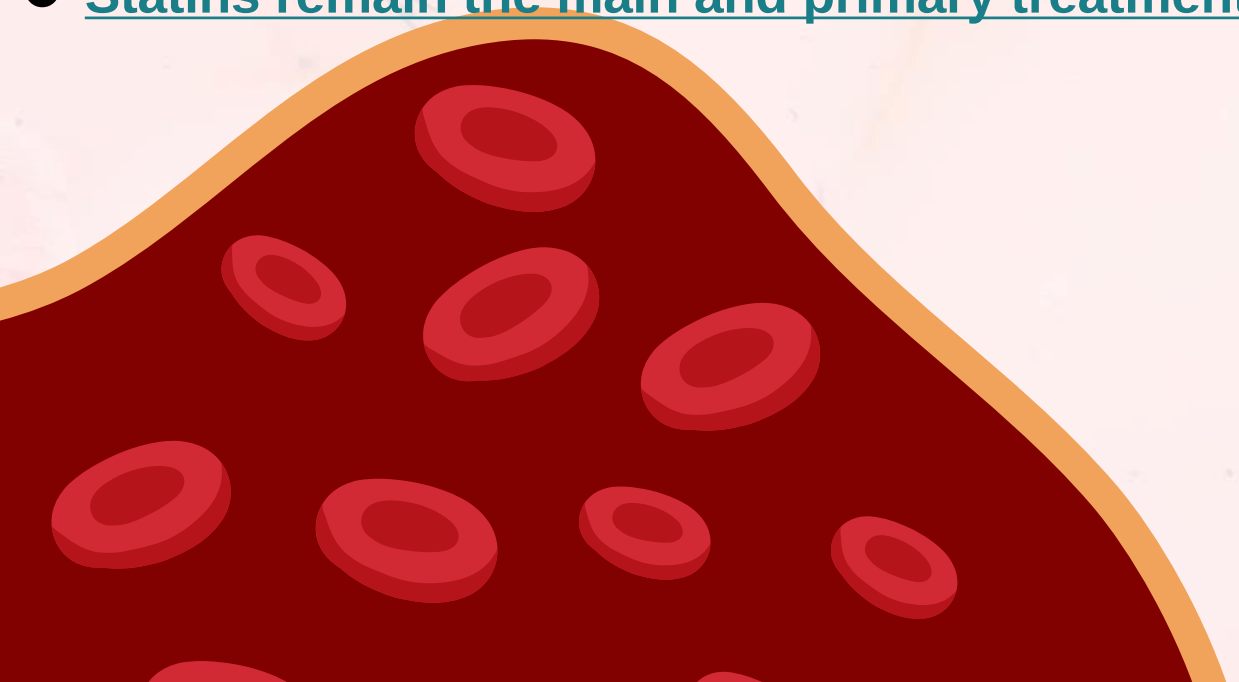
Novel Lipid-Lowering Agents for Reducing Cardiovascular Risk: Beyond Statins

Dr. Malek Zihlif



A small introduction for the lecture:-

- For the last decades , the management of hyperlipidemia was mainly focused around the usage of statins, fibrates , bile acid resins, ezetimibe,….etc.
- But recently, those drugs haven't been providing adequate management for hyperlipidemia , and enough action on LDL.
- So a few new drugs emerged in the field of hyperlipidemia management , and they have new MOA that could provide a more adequate management.
- Statins remain the main and primary treatment, all those new drugs are just Add-on drugs



And if you remember , in the management of hyperlipidemia , the therapy focuses mainly on 2 things:-

1-↓ LDL(eg:therapy for familial hypercholesterolemia)

2- ↓ VLDL(eg:therapy for hypertriglyceridemia)

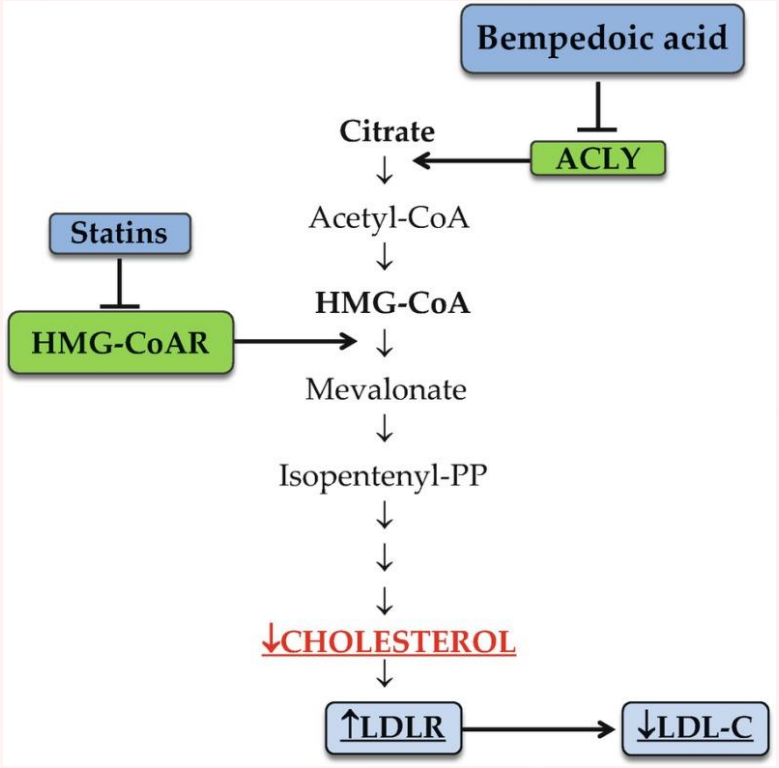
LDL-C LOWERING AGENTS

Bempedoic acid

- 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.
- Thus, inhibition of ACLY leads to a reduction of acetyl-CoA and cholesterol synthesis, resulting in an increased number of LDLRs, causing a subsequent reduction of plasma cholesterol.
- Bempedoic acid is a small molecule that acts as a **selective antagonist of ACLY.**
- It is administered as a prodrug and requires activation by very-long-chain acyl-CoA synthetase-1, which is an enzyme mainly expressed in the liver.

(this will decrease its side effects ,because this enzyme prodrug activator is mainly expressed in the liver)

- This property minimizes the exposure of the active drug to the non-hepatic tissue, such as the skeletal muscle



Notes regarding the previous slide:-

Bempedoic acid is a lipid lowering drug , (mainly LDL) that works on inhibiting cholesterol synthesis via lowering of acetyl coa levels, so they inhibit cholesterol synthesis just like statins, but in a different fashion. Which if you remember will cause the following:-

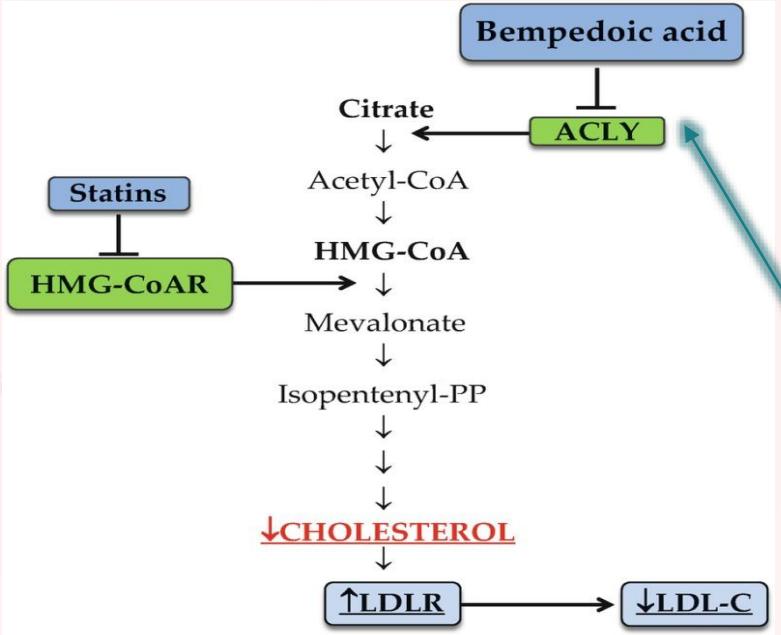
↓Cholesterol → ↑ LDLRs(LDL receptors on the hepatocytes) → ↑ LDL uptake by the liver → ↓ LDL levels in the circulation.

ALSO: ↓Cholesterol → ↓ VLDL via feedback inhibition.(the doctor did not mention this point ,its extra)

ALSO: ↑ HDL

- The maximum efficacy of this drug is around a 25-30% decrease of LDL(Statins have higher efficacy)

So what is the mechanism of inhibiting cholesterol synthesis in this drug?
Bempedoic acid is a prodrug, it's active metabolite that forms by activation through very-long chain fatty acyl coa synthetase inhibits the enzyme ATP citrate lyase(ACLY) via selective antagonism, this enzyme is responsible for the ATP – dependent conversion of citrate to Acetyl Coa, which is needed for the formation of the intermediate HMG Coa .(statins inihibit the next step in this pathway , HMG coa reductase)



As a compensatory mechanism,the stomach and the intestinal (duodenal) absorption of cholesterol increases, so its good to combine this drug with Ezetimibe(cholesterol absorption inhibitor).

Bempedoic acid

It inhibits (actually competes for) the transporter for uric acid

- Bempedoic acid was associated with **increase** of blood urea nitrogen, creatinine, and **uric acid**. It also resulted in a **decrease** in **hemoglobin.** → **can cause anemia**
- Gout incidence was **higher** in the bempedoic acid group compared with the placebo group**(3% of patients taking it suffer from Gout)**
- New-onset diabetes/hyperglycemia incidence was **lower** in the bempedoic acid group compared with that in the placebo group

PCSK9 inhibition by monoclonal antibodies

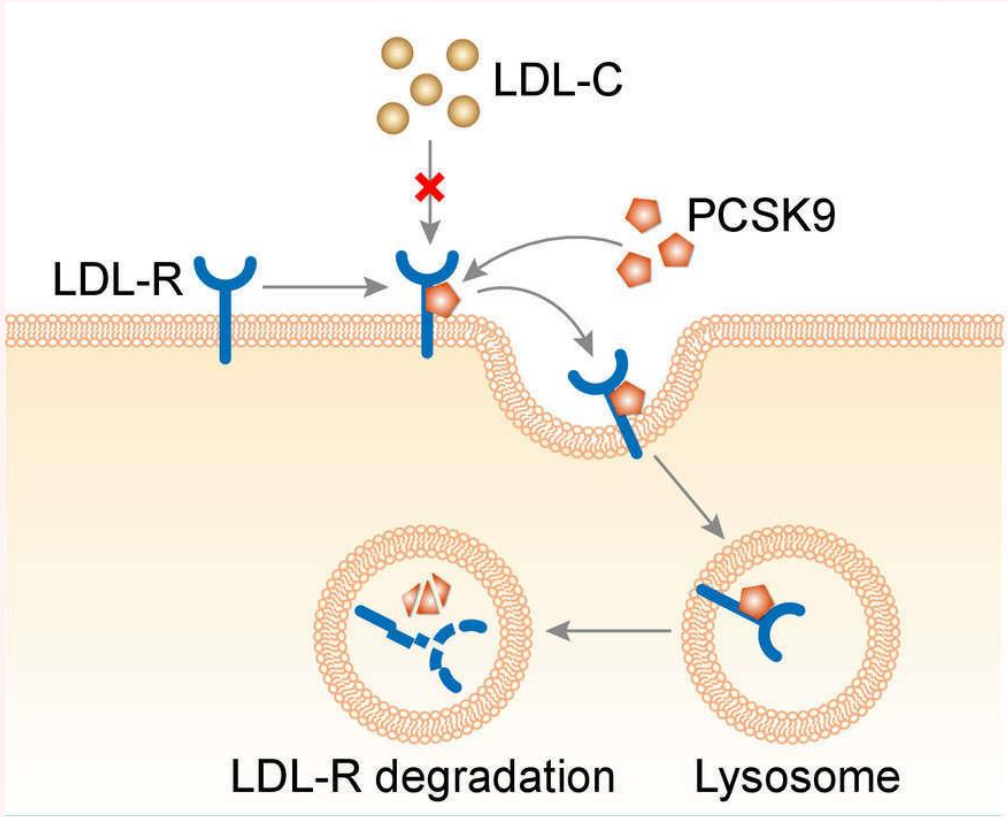
- Proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme predominantly produced in the liver, binds to the LDL receptor (LDLR) present on the surface of the hepatocytes, leading to its degradation and **a subsequent increase in plasma LDL-C levels**

PCSK9 increases the lysosomal degradation of LDL-R which will consequently cause increased LDL-C levels, so we work on inhibiting this PCSK9 dependent lysosomal degradation to increase the LDR-R levels.

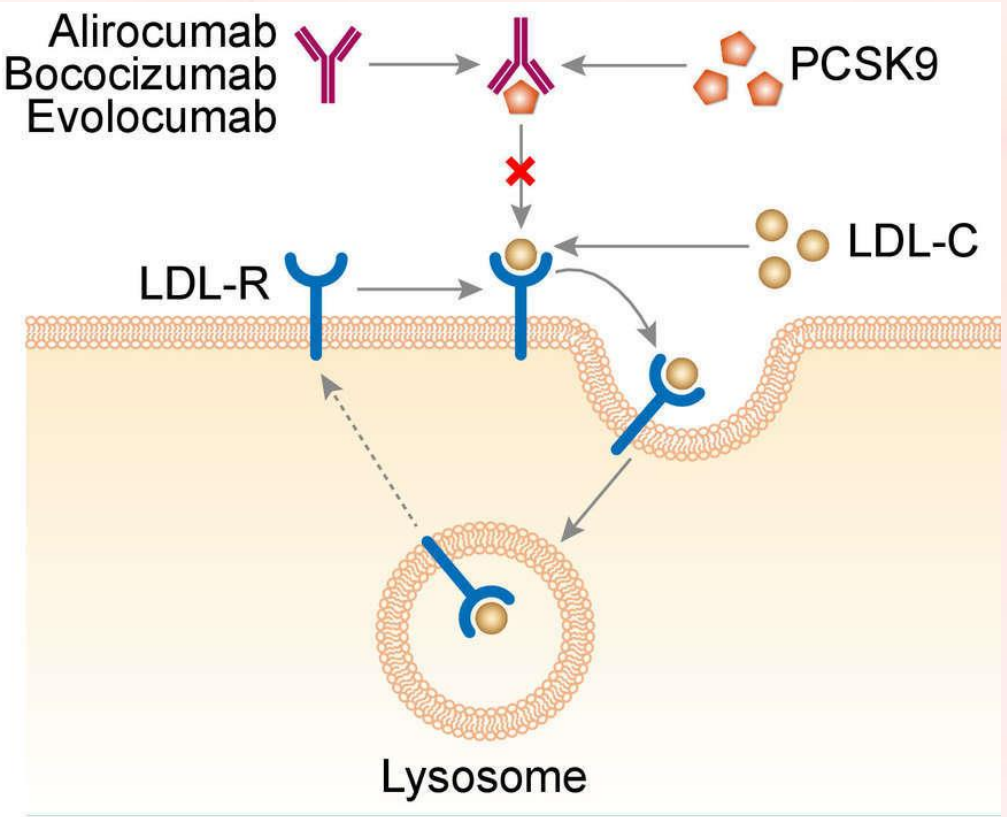
- Thus, inhibition of PCSK9 causes an increase in LDLR number and a subsequent decrease in plasma LDL-C levels
- Among the several monoclonal antibodies developed against PCSK9, **evolocumab and alirocumab** have been approved for clinical use

They can be taken with statin to increase its acitivity

What's good about those drugs is that they give us the wanted effect of increased LDL-Rs but without the side effects of myopathy, rhabdomyolysis, hyperuricemia…..etc , EXCEPT for a flu like syndrome from those monoclonal antibodies that goes within around 1 week



Physiology of PCSK9



Mechanism of action of anti-PCSK9 mAb

Abbreviations
PCSK9: proprotein convertase subtilisin kexin type 9
LDL-C: low-density lipoprotein cholesterol
LDL-R: low-density lipoprotein receptor
mAb: monoclonal antibody

PCSK9 inhibition by RNA silencing

This drug here inhibits the PCSK9 from the point of synthesis , the previous drugs were monoclonal antibodies, that inhibit and bind the enzyme itself.

Basically the antisense oligonucleotide is bound to the triantennary N-acetylgalactosamine carbohydrates, this carb binds a receptor on the liver that facilitates the entrance of the siRNA antisense oligonucleotide.

- **Inclisiran** is a synthetic small interfering RNA (siRNA), which works by targeting the PCSK9 mRNA, and is conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc), which targets the siRNA to the liver
- Inclisiran shows comparable effects to that of PCSK9 monoclonal antibodies
- Side effect: The inclisiran group reported a higher rate of injection-site reaction compared with the placebo group (17.0% vs. 1.7%), which was graded as mild

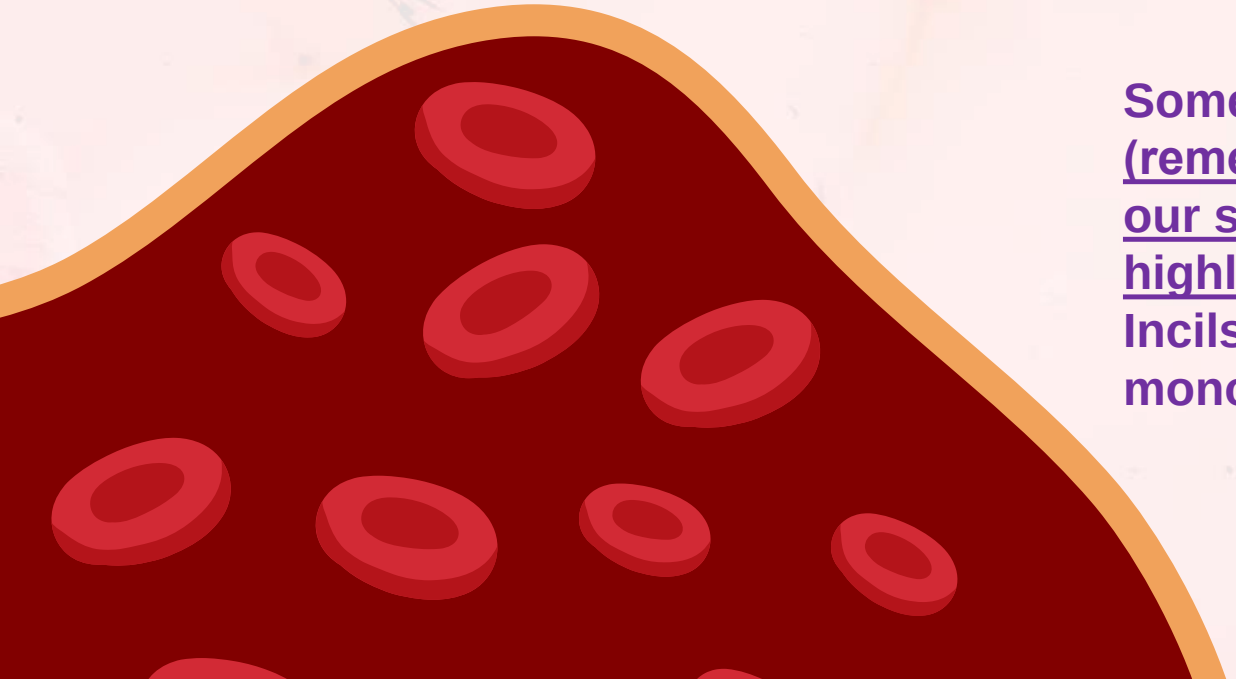
Notes on the previous slide:-

Inclisiran inhibits the PCSK9 from the point of synthesis , the previous drugs were monoclonal antibodies, that inhibit the enzyme itself.

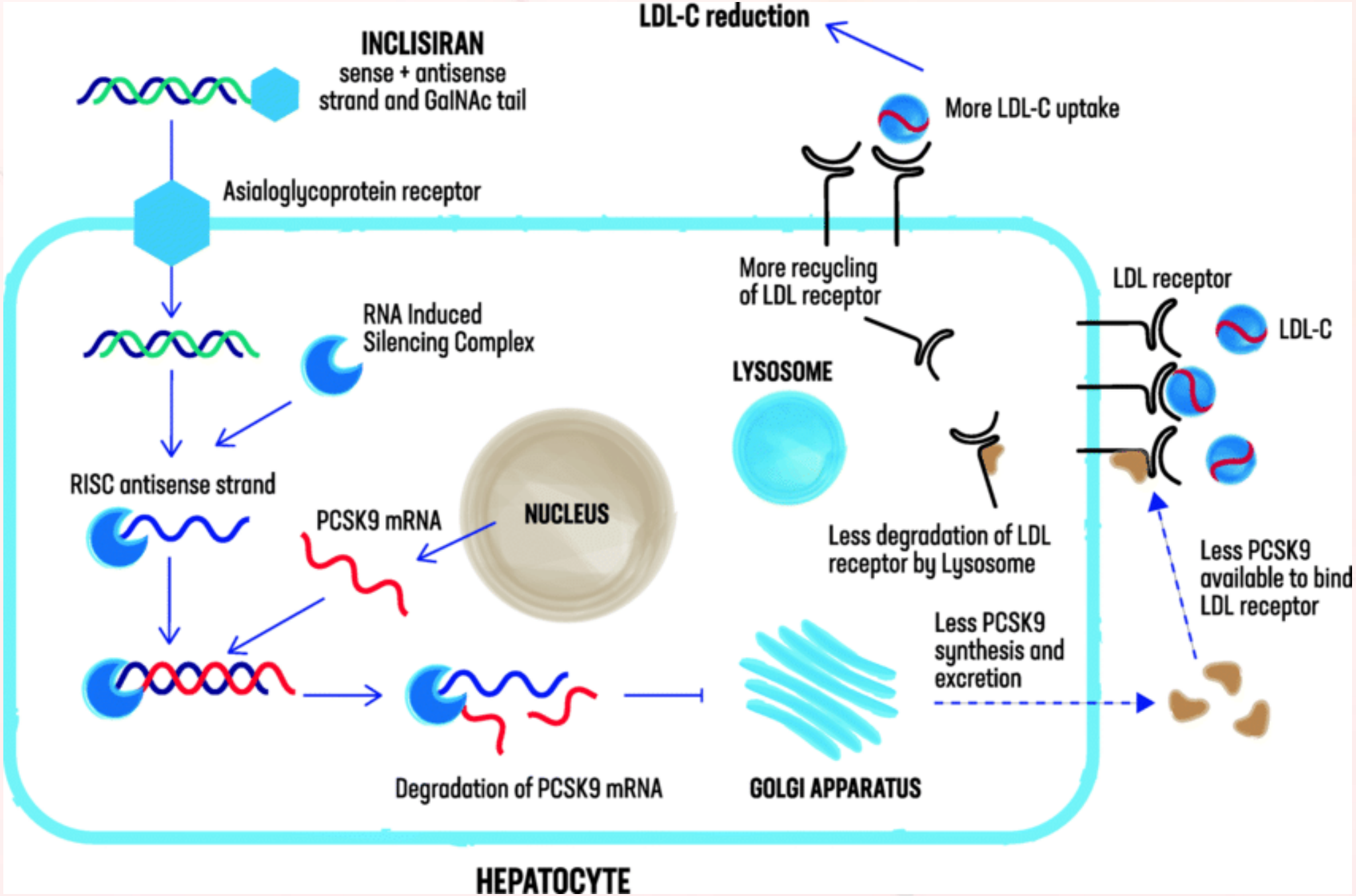
- this drug is a small interfering RNA, basically a small sequence of double stranded RNA (22-26 nucleotides), and its gonna target the mRNA responsible for the synthesis of the PCSK9 enzyme.

And the drug is also conjugated with GalNAc , which is just for the transportation of this siRNA to the liver.

The drug realistically has no side effects, and is very expensive costs around 3,000 jds per syringe



Some therapeutics regarding those PCSK9 inhibitors:
(remember, the doctor said therapeutics aren't important for our stage,this is just what he mentioned in the lecture but I highly doubt he will ask about it)
Incilsiran is taken 3 times a year and has a loading dose, monoclonal antibodies also have a loading dose.

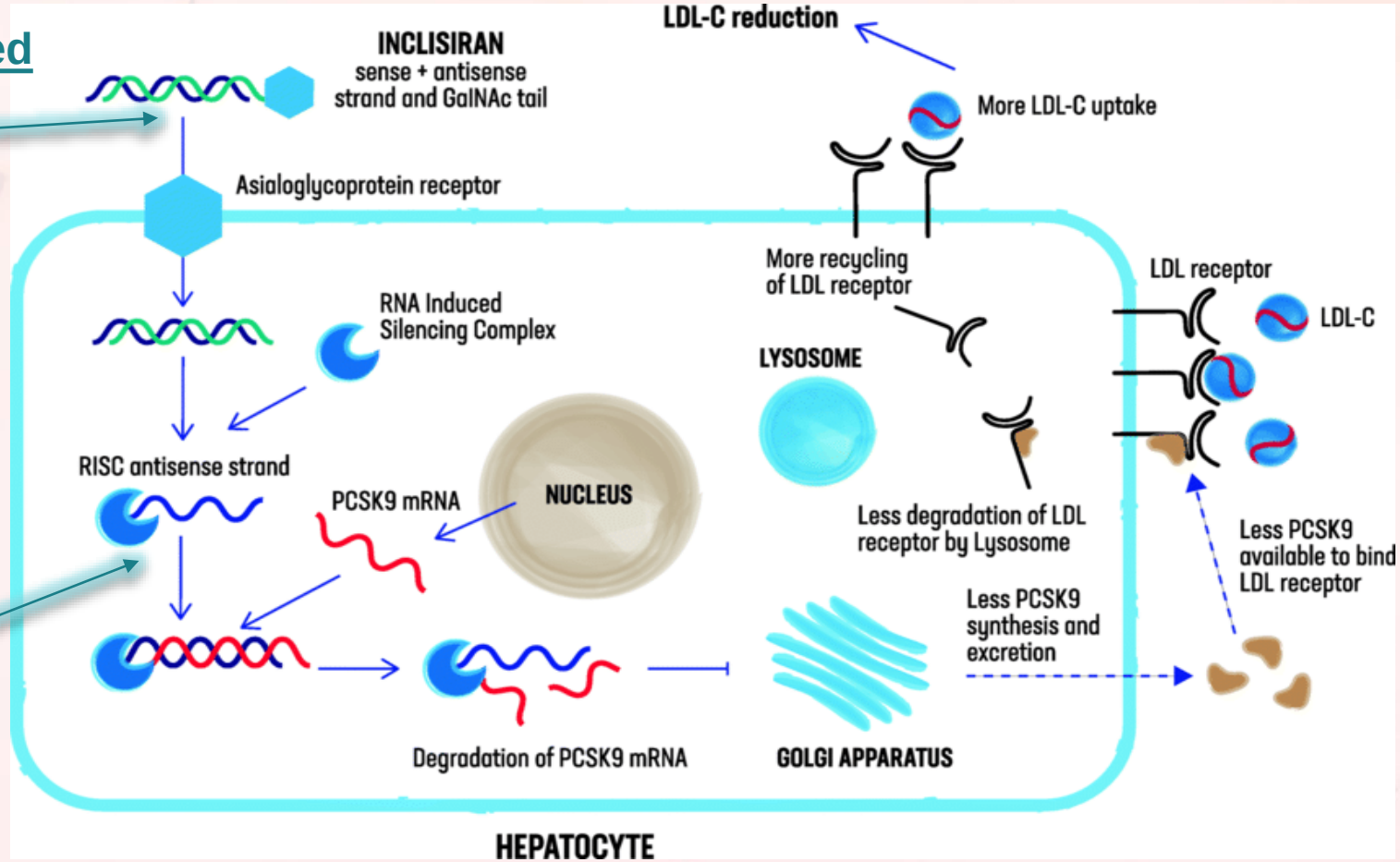

LDL-C reduction
INCLISIRAN
sense + antisense strand and GalNAc tail
More LDL-C uptake
Asialoglycoprotein receptor
More recycling of LDL receptor
LDL receptor
LDL-C
RNA Induced Silencing Complex
LYSOSOME
RISC antisense strand
PCSK9 mRNA
NUCLEUS
Less degradation of LDL receptor by Lysosome
Less PCSK9 available to bind LDL receptor
Less PCSK9 synthesis and excretion
Degradation of PCSK9 mRNA
GOLGI APPARATUS
HEPATOCYTE

Some notes regarding the MOA of incilsiran:

This double stranded siRNA (incilsiran) is conjugated GalNAc and gets transported into the hepatocyte , after entering the cell it binds with a complex called RNA induced silencing complex (RISC), **this complex will take the antisense portion of inclisiran (the strand complementary to PCSK9 mRNA)**, and this strand is compatible with the single stranded PCSK9 mRNA, which will result in binding to the mRNA, and then it's degradation RISC

Double stranded siRNA

single strand of siRNA that is compatible with the mRNA of the PCSK9 enzyme (red strand)



ApoC-III inhibitor

- 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.
- **Those drugs inhibit the inhibitor (ApoC-III) of TG (Triglyceride) lipolysis(catabolism) by LPL.**
- loss-of-function mutations in the APOC3 gene are associated with 40% lower plasma TG levels and a 40% lower risk of CVD

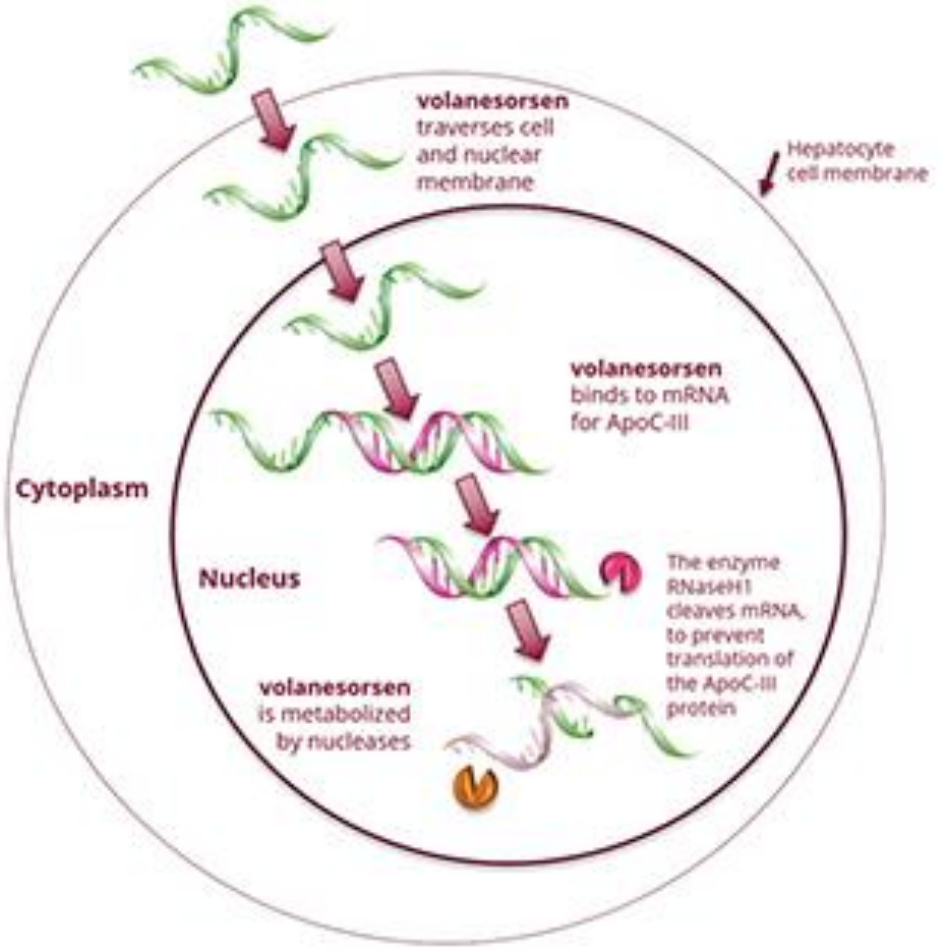
ApoC-III inhibitor: Volanesorsen

- Volanesorsen is an **antisense oligonucleotide (ASO)** targeting **apoC3 mrna (it's a siRNA just like incilsiran, usually double stranded)**
- **It basically enters the cell and inhibits the mRNA responsible for the synthesis of ApoC-III**
- Volanesorsen has been tested in patients with elevated plasma TG levels and in patients with familial chylomicronemia syndrome (FCS), an autosomal recessive disease of chylomicron metabolism
- **Its also used in hypertriglyercidemias**
- In 2019, volanesorsen was approved by the European Union (EU) for the treatment of adult patients with FCS

- Common adverse events are thrombocytopenia **(little incidence)** and injection-site reactions

Volanesorsen Mechanism of Action

Preventing Formation of ApoC-III by a Second Generation Antisense Oligonucleotide (ASO)



Attributes of Antisense Drugs

- Highly specific, with reduced potential for off-target binding
- No known drug/drug interactions, not metabolized by CYP450 pathways
- Unable to cross placenta and blood/brain barrier

ANGPTL3 inhibitor

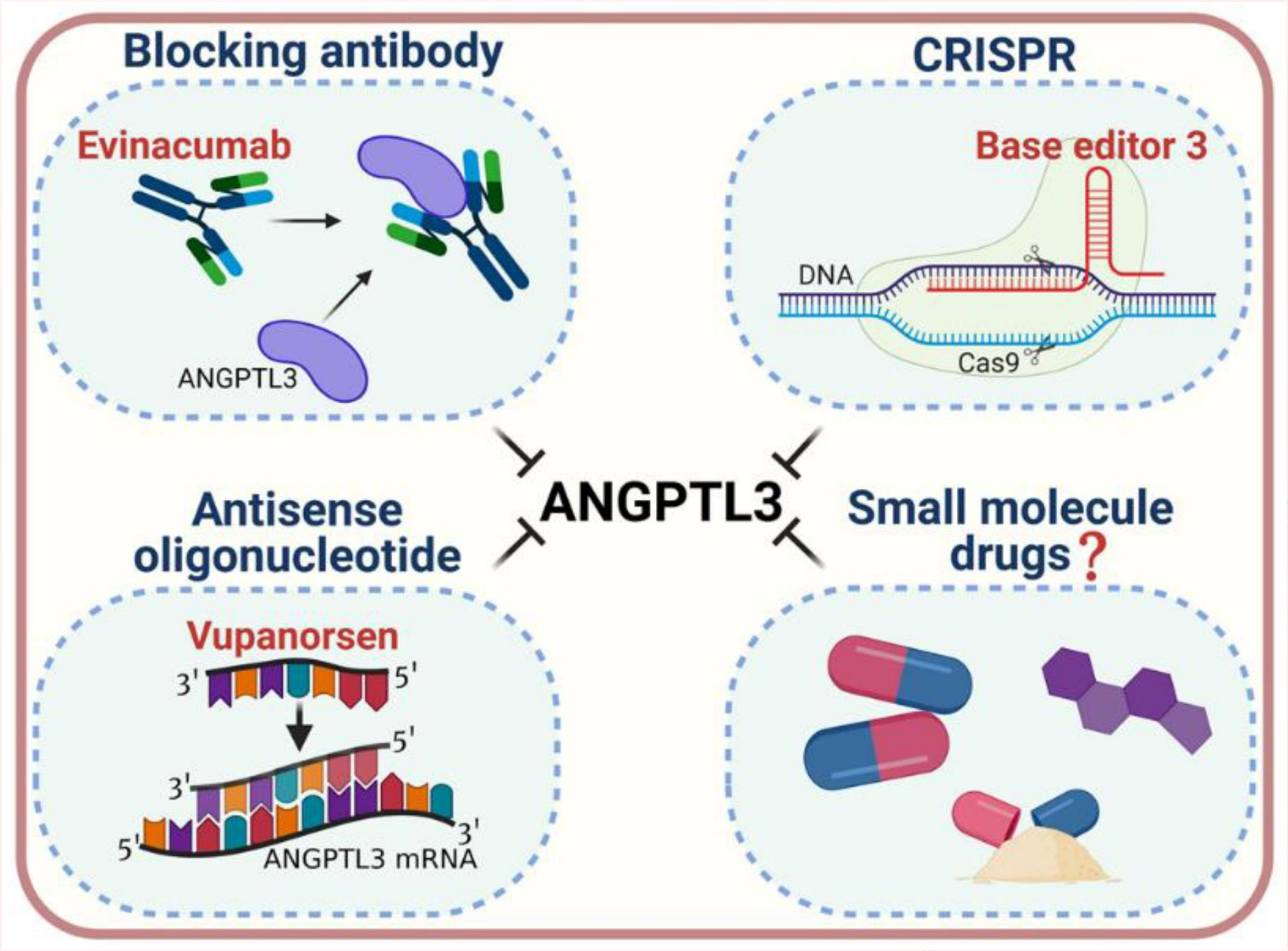
- ANGPTL3 regulates plasma TG and HDL-C levels by inhibiting lipoprotein lipase (LPL) and endothelial lipase, respectively.
- Inhibition of ANGPTL3 preserves the function of LPL and EL with a subsequent decline in TG, LDL-C and HDL-C plasma levels **independently of LDLR function** **(most effect is on the TG)**
- Therefore, it was proposed that blocking ANGPLT3 might produce a beneficial effect on cardiovascular risk and future outcomes.
- therapies targeting ANGPTL3 were developed by two mechanisms:

1. **Evinacumab** a monoclonal antibody neutralizing levels of ANGPTL3 in the serum.

Influenza like effect was observed in 11%

1. **Vupanorsen** an antisense oligonucleotide inhibiting production in hepatocytes **(siRNA same as the last drug (volanosoren) except the target here is ANGPTL3)**

They basically have no side effects except for the flu like syndrome cause by the monoclonal antibody (Evinacumab)


Blocking antibody
Evinacumab
ANGPTL3
CRISPR
Base editor 3
DNA
Cas9
ANGPTL3
Antisense oligonucleotide
Vupanorsen
3'
5'
5'
3'
3'
5'
ANGPTL3 mRNA
Small molecule drugs?

This table is just a summary for all new drugs we took, but its just for guidelines because we didn't take all the drugs here.

Agent	Mechanism of Action	Main Lipid Lowering Effect	Administration Scheme	Side-Effects	Comment
Statin	HMG-CoA inhibition	LDL - C	1x/day p.o.	Myopathy, increased liver enzymes	Side-effects are rare, novel statins like rosuvastatin and atorvastatin can be taken in the morning because of long t 1/2
Ezetimibe	NPC1L1 protein inhibition	LDL-C	1x/day p.o.	Diarrhoea	Side-effects are rare
PCSK9i (alirocumab/ evolocumab)	PCSK9 inhibition	LDL-C	2x/month (1x/ month) s.c.	Injection site reactions	Side-effects are rare, not more than placebo
Inclisiran	siRNA targeting mRNA PCSK9	LDL-C	2x/year s.c.	Injection site reactions	Side-effects are rare, not more than placebo (still under investigation)
Bempedoic acid	Inhibiting ACL and AMPK	LDL-C	1/day p.o.	Not greater than placebo	Alernative to SAMS?
Icosapent ethyl	LPL?	TGs	1/day p.o.	?	Benefit of long-term use of this agent still needs to be proven; many pleiotropic effects
Volanesorsen	Antisense oligonucleotide to apo C-III	TGs	2x/year s.c.	Thrombocytopenia and injection-site reactions	Treatment of ultra rare LPL deficiency
ANGPTL3	Monoclonal anti-ANGPLT3 antibody and ASO	TGs, LDL-C	2x/year s.c.?	Not yet fully determined	Studies are ongoing
Pemafibrate	Peroxisome proliferator-activated receptor alpha modulator	TGs	1/day p.o.	Liver enzymes?	Clinical data as well as long-term efficacy and safety need to be investigated
Pelacarsen	ASO to apolipoprotein(a)	Lp(a)	2x/year s.c.?	?	The agent is in phase III trial

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; LDL-C, Low density lipoprotein cholesterol; NPC1L1, Niemann-pick-C1 like-1 protein; PCSK9i, inhibitor of proprotein kexin serin convertase type 9; p.o., peroral therapy; s.c., subcutaneous therapy; ACL, Adenosine triphosphate-citrate lyase; AMPK, adenosine monophosphate-activated protein kinase; SAMS, statin associated muscular symptoms; TGs, Triglycerides; LPL, lipoprotein-lipase; Apo-CIII, Apolipoprotein CIII; ANGPTL3, Angiopoietin-Like 3; ASO, anti sense oligonucleotide; Lp(a), lipoprotein (a).
Notes: ? indicates unknown side effects.

كانت هذه اخر محاضرة فارما لجهاز القلب والأوعية الدموية،
بارك الله في وقتكم و في جهودكم وان شاء الله أعلى العلامات في الامتحان،بالتوفيق

اللهم يامن لا يهزم جنده ولا يخلف وعده، ولا إله غيره، كُن لأهلنا فى فلسطين عونًا ونصيرًا ومعينًا وظهيرًا.

Thank You