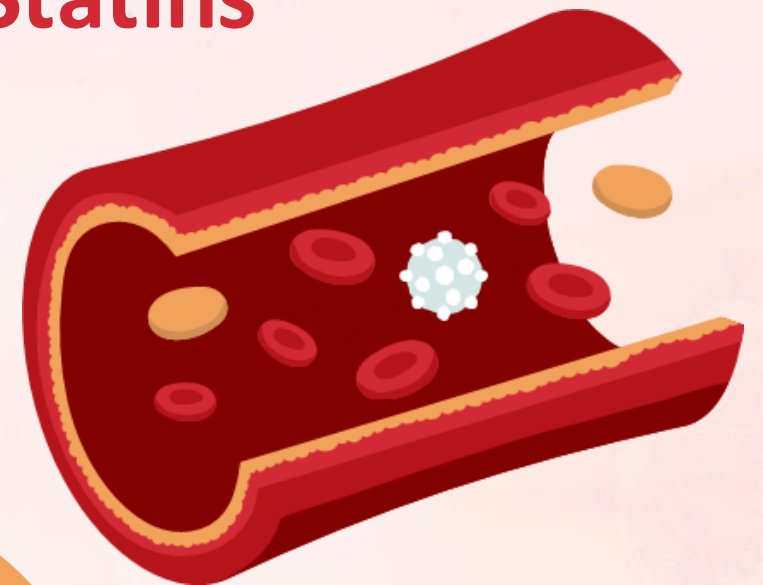


Novel Lipid-Lowering Agents for Reducing Cardiovascular Risk: Beyond Statins

Dr. Malek Zihlif

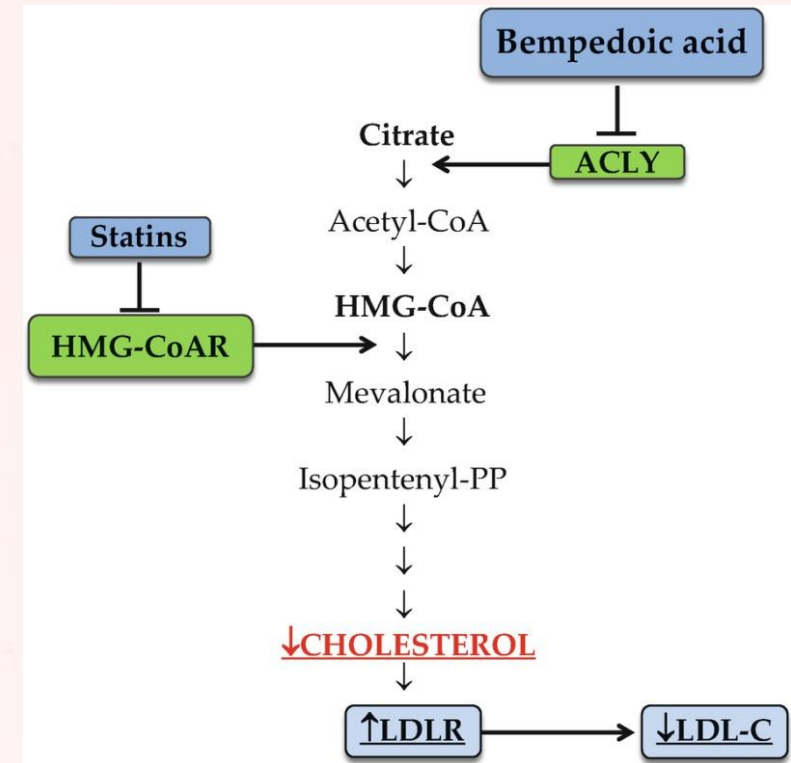


LDL-C LOWERING AGENTS



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





Bempedoic acid

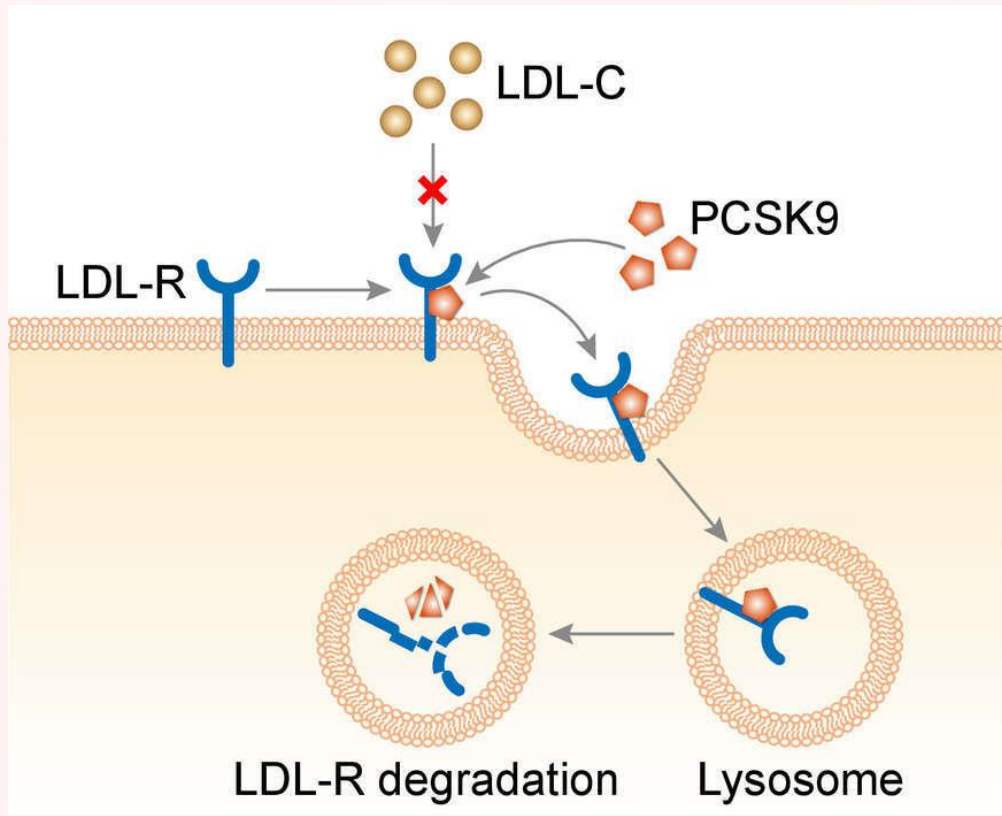
- Bempedoic acid was associated with **increase** of blood urea nitrogen, creatinine, and uric acid. It also resulted in a **decrease** in hemoglobin.
- Gout incidence was **higher** in the bempedoic acid group compared with the placebo group
- New-onset diabetes/hyperglycemia incidence was **lower** in the bempedoic acid group compared with that in the placebo group



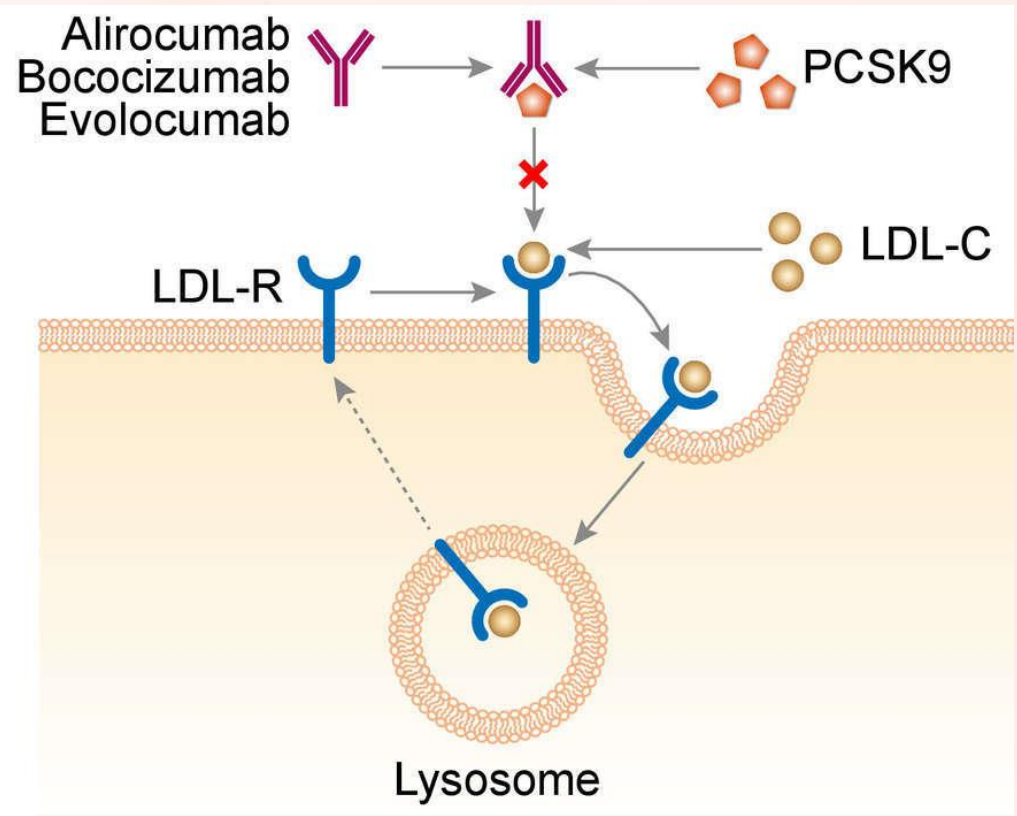
PCSK9 inhibition by monoclonal antibodies

- 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
- 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





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

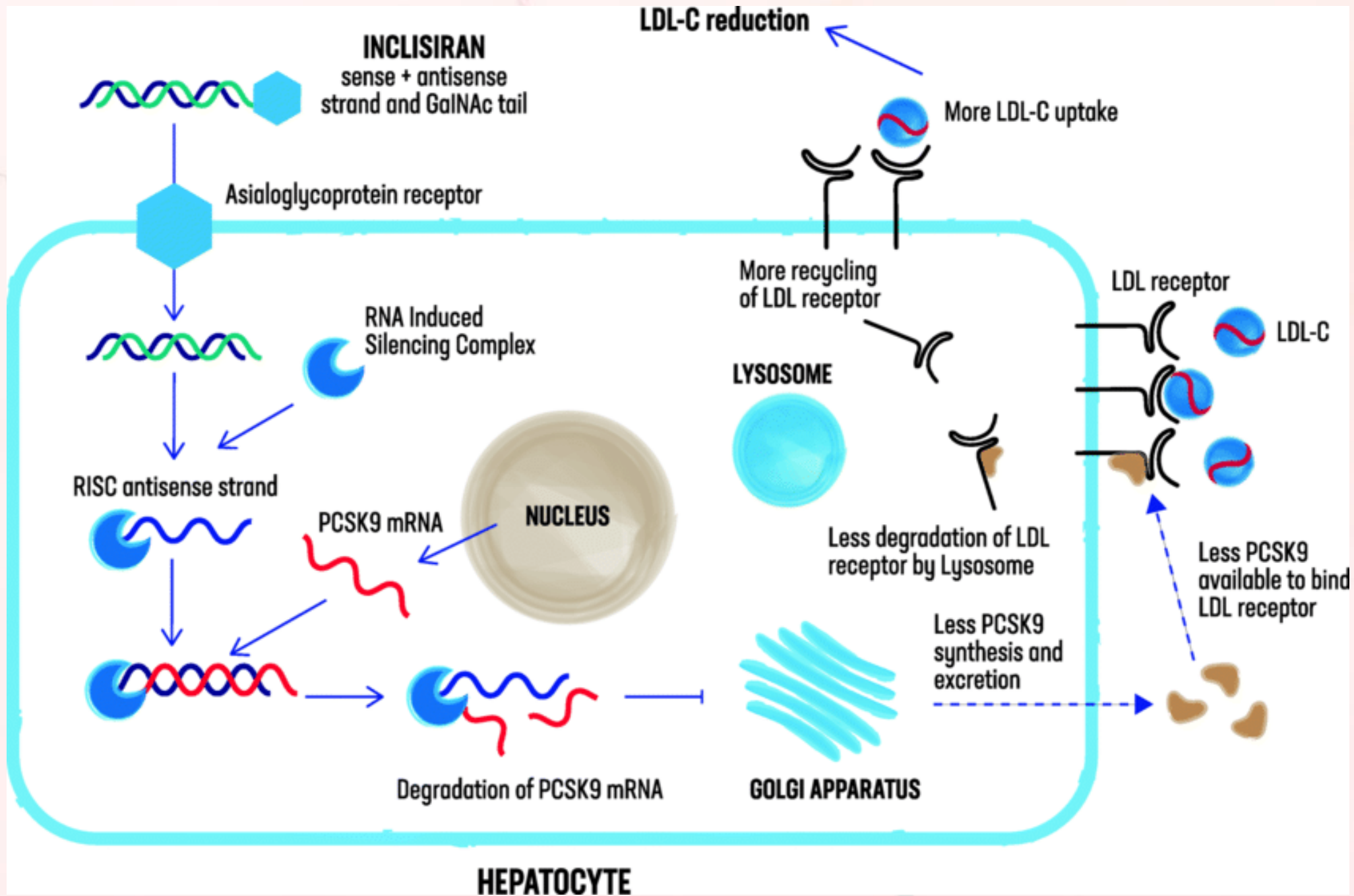
mAb: monoclonal antibody



PCSK9 inhibition by RNA silencing

- **Inclisiran** is a synthetic small interfering RNA (siRNA), which works by targeting the PCSK9 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





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.
- loss-of-function mutations in the APOC3 gene are associated with 40% lower plasma TG levels and a 40% lower risk of CVD



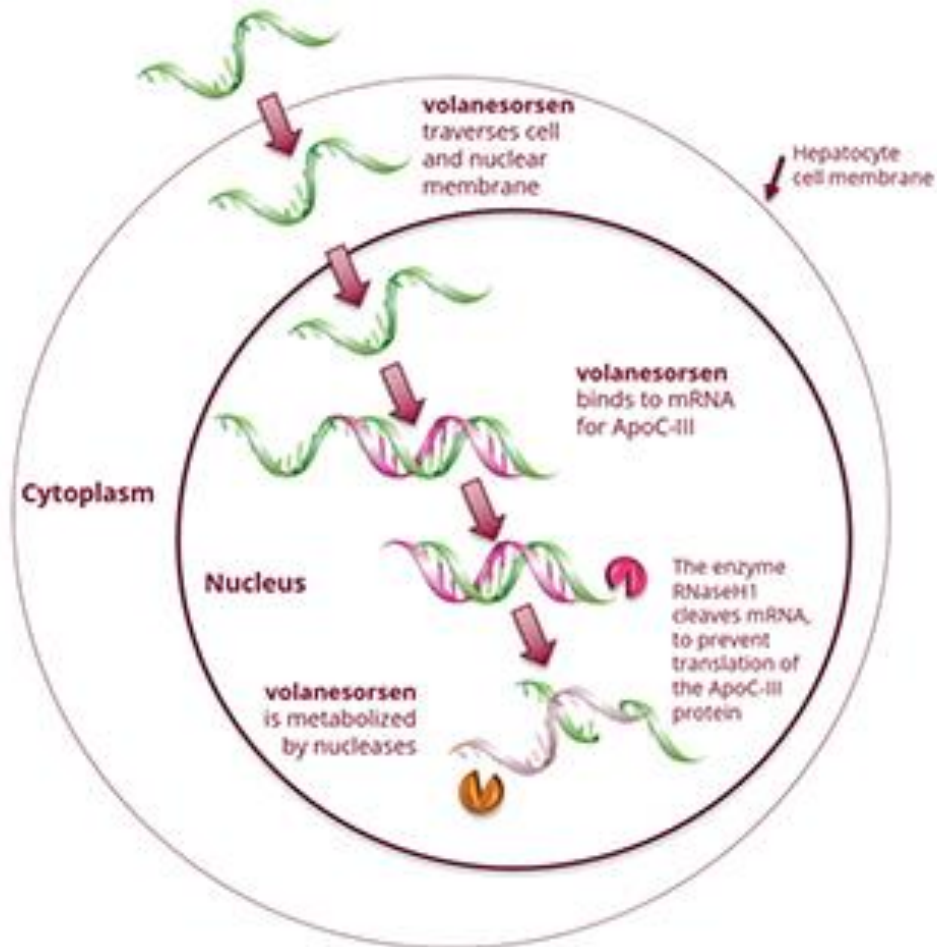
ApoC-III inhibitor: Volanesoren

- Volanesorsen is an **antisense oligonucleotide (ASO)** targeting **apoC3 mrna**
- 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
- In 2019, volanesorsen was approved by the European Union (EU) for the treatment of adult patients with FCS
- Common adverse events are thrombocytopenia 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



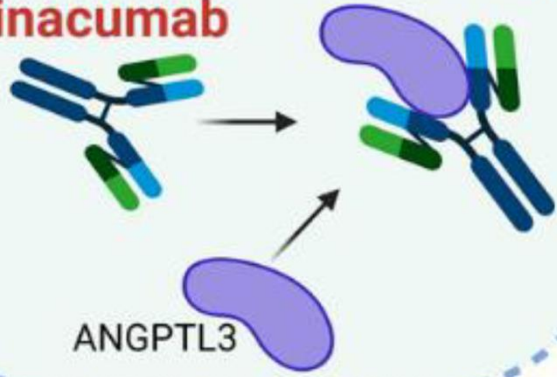
ANGPTL3 inhibitor

- 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
- Therefore, it was proposed that blocking ANGPTL3 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 in the serum
Influenza like effect was observed in 11%
 1. **Vupanorsen** an antisense oligonucleotide inhibiting production in hepatocytes



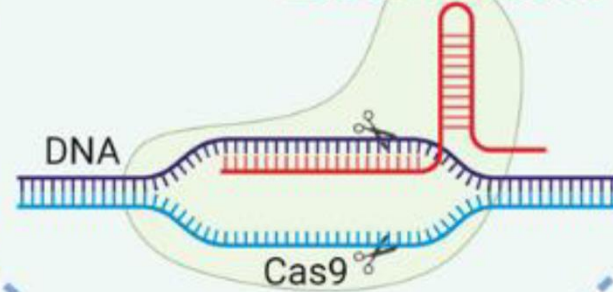
Blocking antibody

Evinacumab

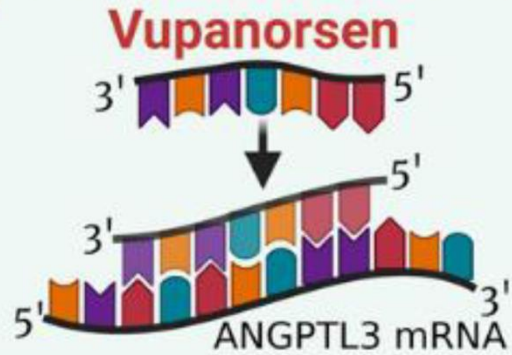


CRISPR

Base editor 3



Antisense oligonucleotide



ANGPTL3

Small molecule drugs ?



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	Alternative 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 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, Angiotensin-Like 3; ASO, anti sense oligonucleotide; Lp(a), lipoprotein (a).

Notes: ? indicates unknown side effects.

