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

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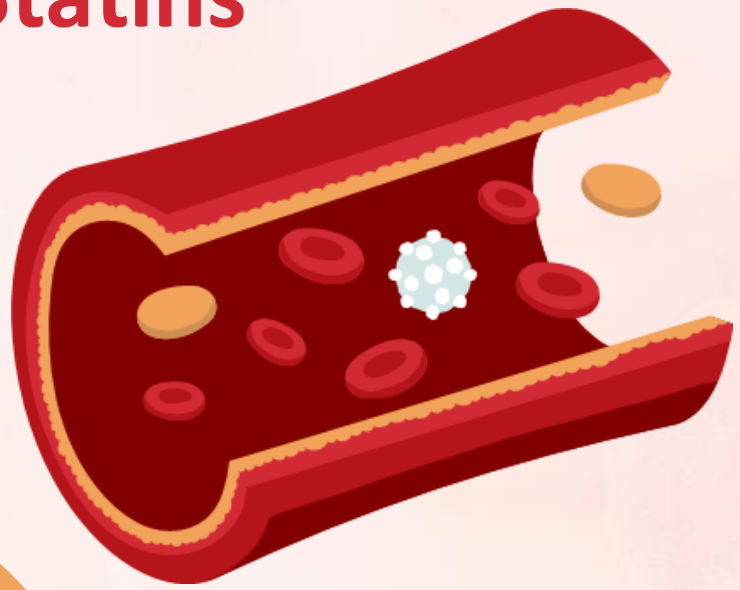
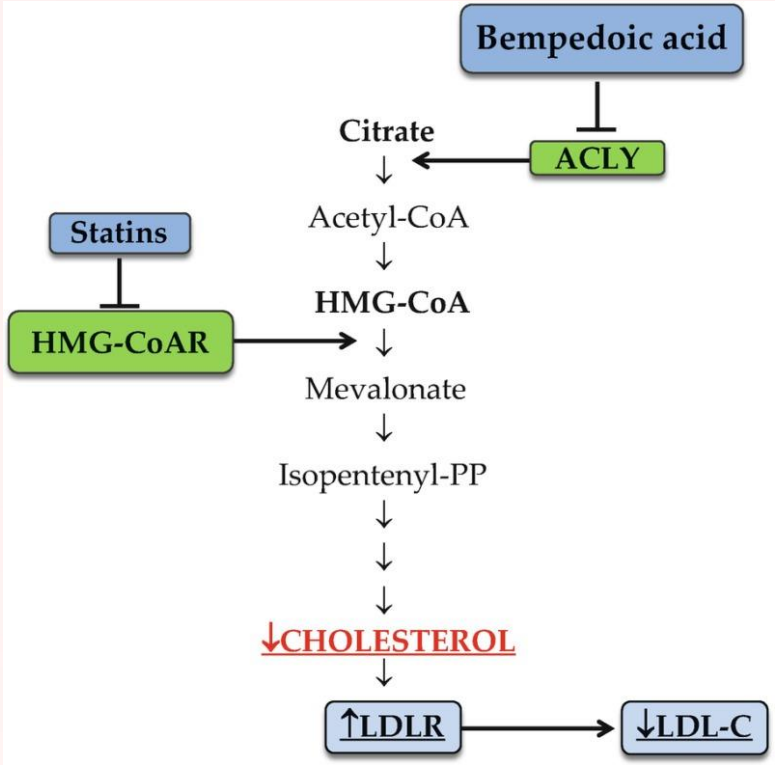


LDL-C LOWERING AGENTS

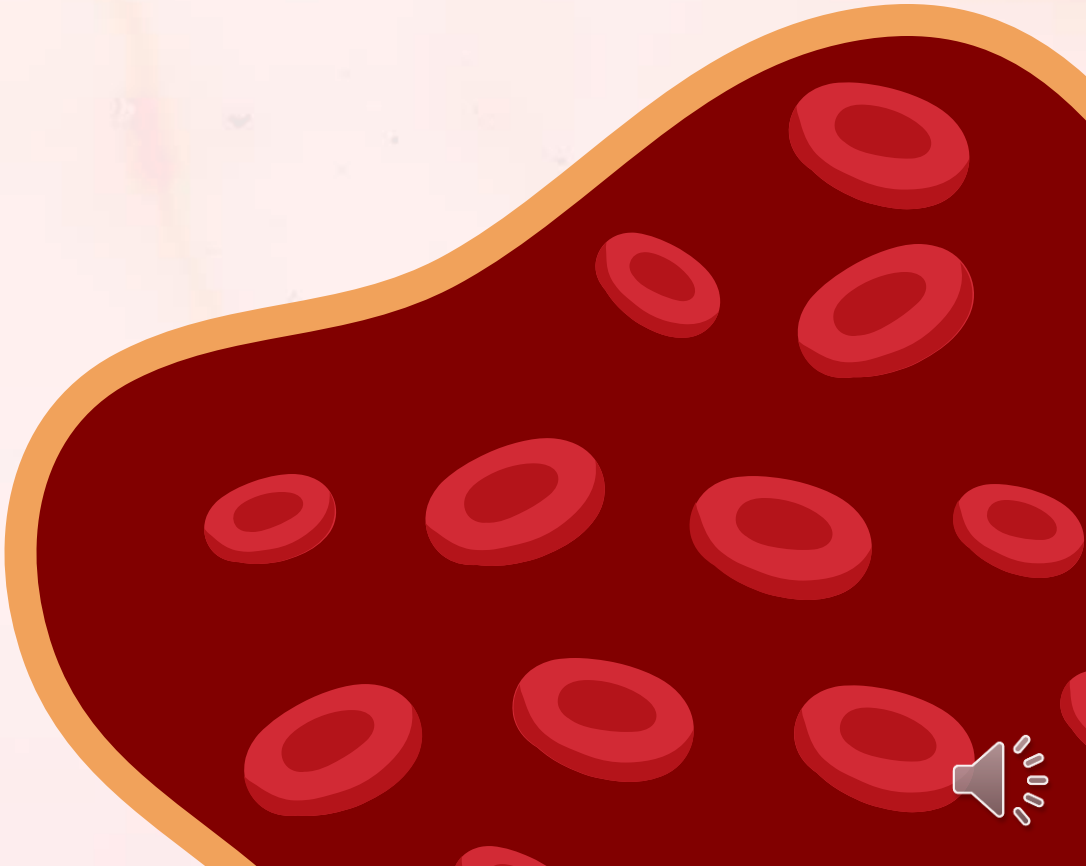
Bempedoic acid

- 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



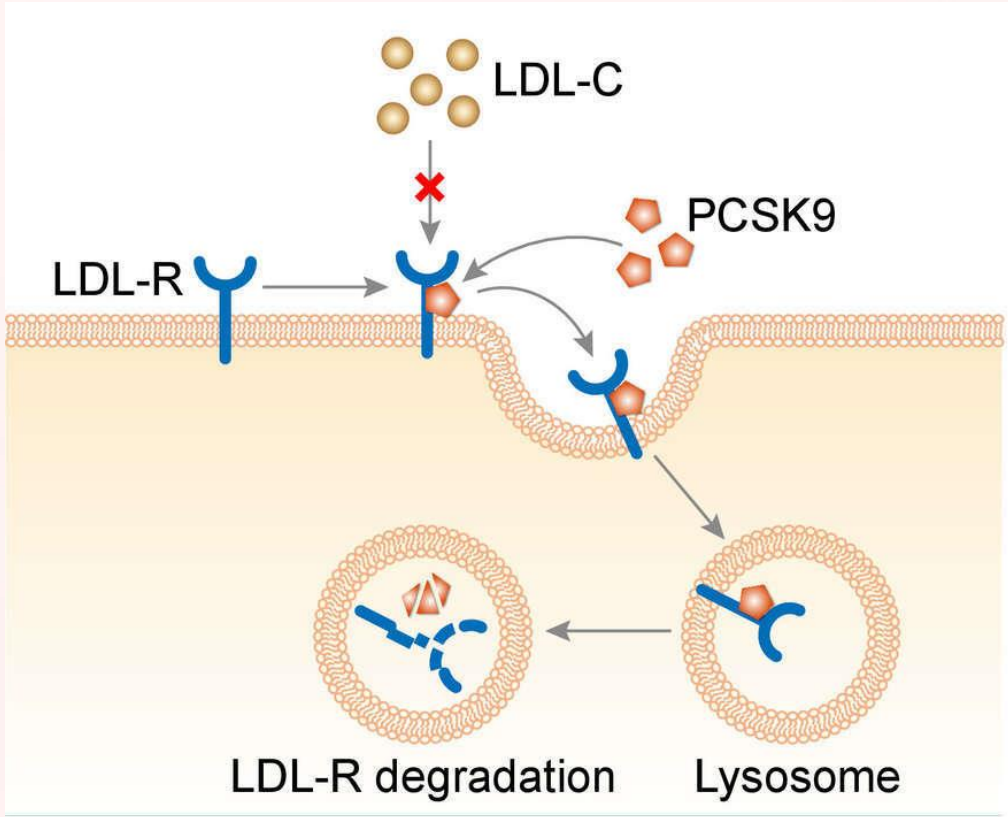
Bempedoic acid

- 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

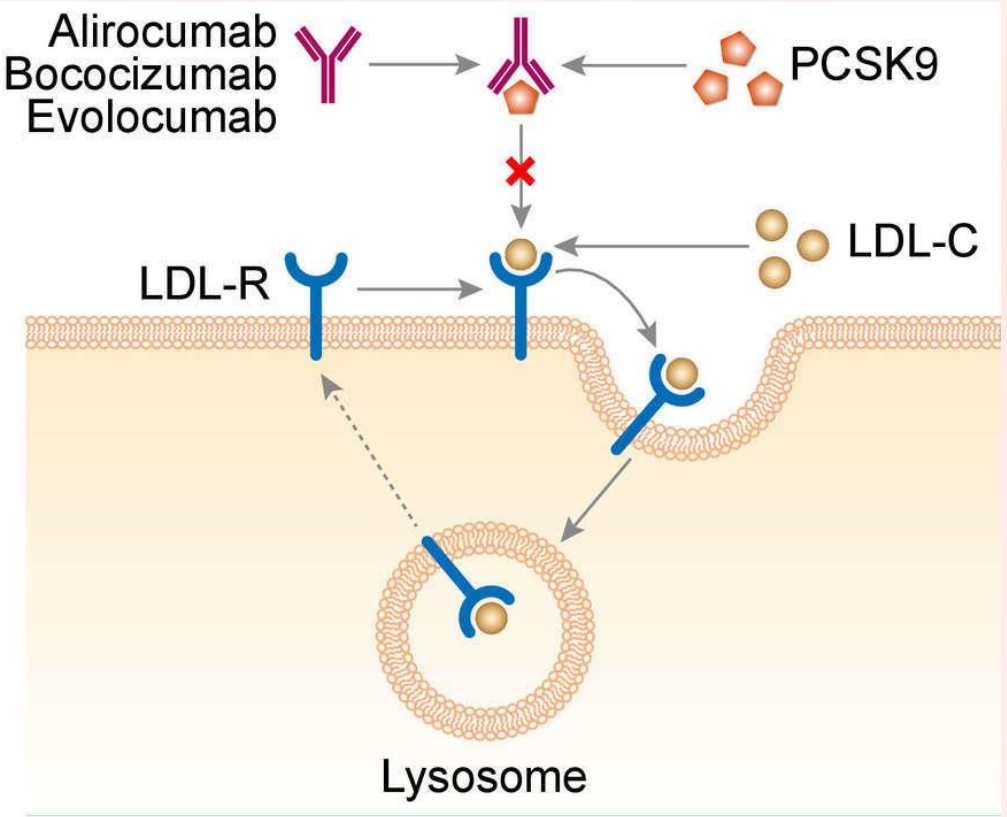


PCSK9 inhibition by monoclonal antibodies

- 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

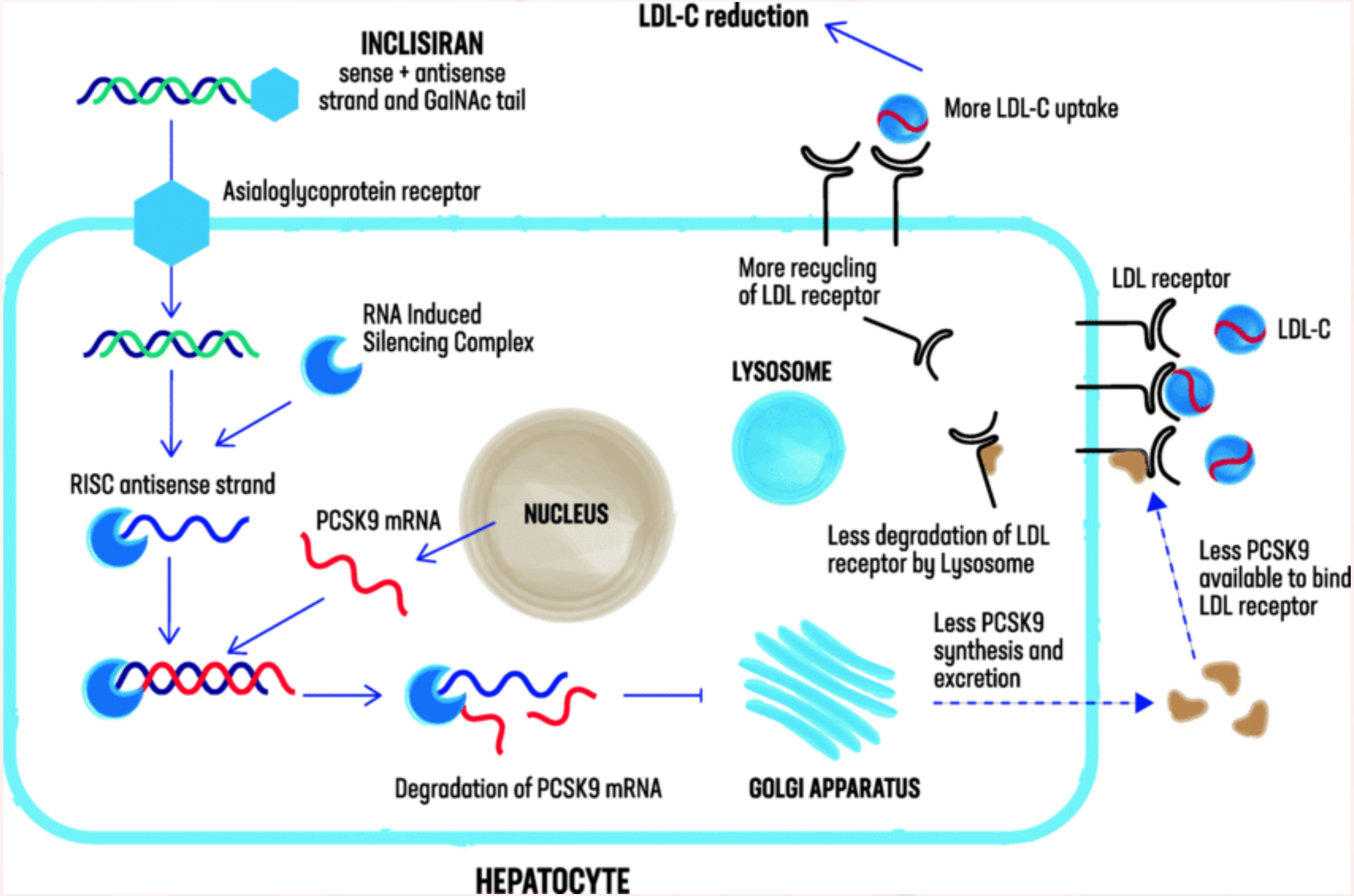


Mechanism of action of anti-PCSK9 mAb

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


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

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**

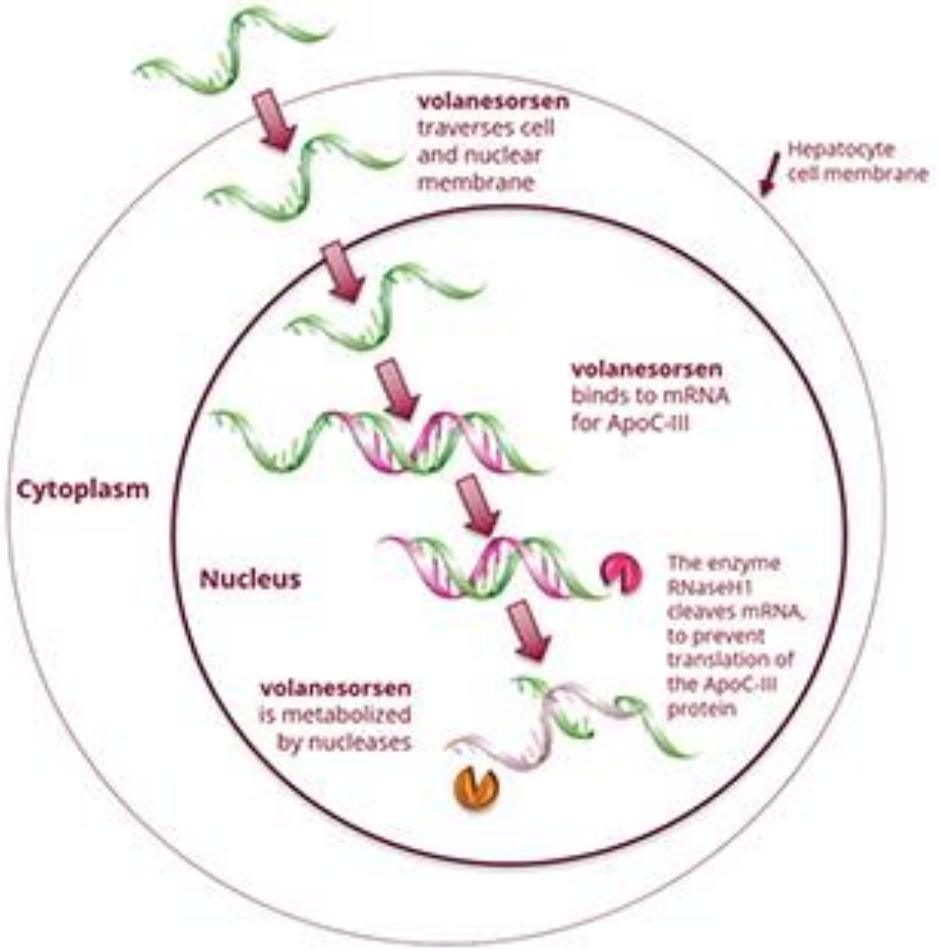
- Volanesorsen has been tested in patients with elevated plasma TG levels and in patients with familial chylomicronemia syndrome (FCS), an autosomal recessive disease of chylomicron metabolism

- 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

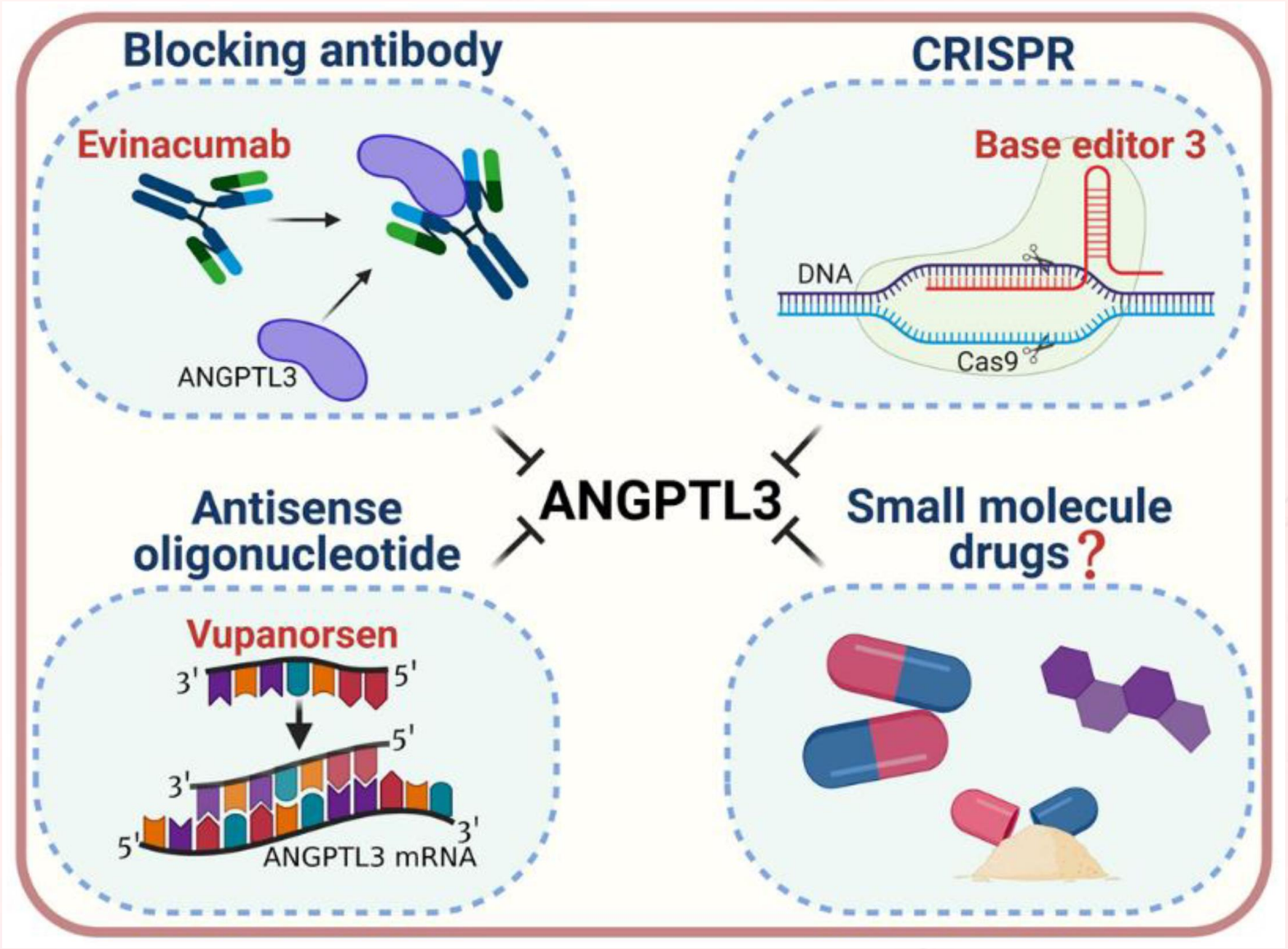
ANGPTL3 inhibitor

- 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 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 in the serum

Influenza like effect was observed in 11%

1. **Vupanorsen** an antisense oligonucleotide inhibiting production in hepatocytes


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?

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.