LDL-C Lowering agents

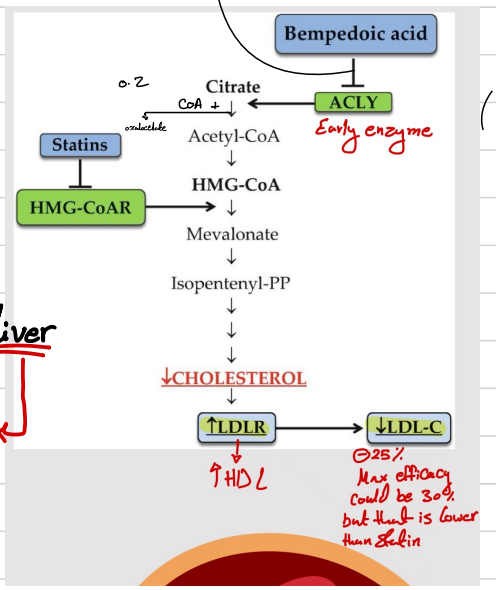
1 Bempedoic Acid :

* Small molecul that act as a selective antagonist of ACLY

* ADministered as a prodrug => Activated by (very-Long-chain acyl-CoA synthetase-1) → Mainly expressed in liver

* thats Minimize the exposure of active Drug to non-Hepatic tissue ∴ Activated only in liver

↓Acetyl-CoA → ↓cholesterol Synthesis → ↑#of LDL-R → ↓LDL-C (plasma cholesterol)



SEs

- ↑ transporter for uric acid ⟹
  - ↑ blood urea Nitrogen
  - ↑ creatinine
  - ↑ uric acid → Especially
- ↓ Hemoglobin → May produce Anemia
- May happen with 3% of the population

bempedoic-A vs placebo

Higher ← Gout incidence → Lower

Lower ← Newonset Diab/Hyperglycemia → Higher

- May have Muscle pain (Not that much)

* in previous drugs we ↓ cholesterol Synthesis ∴ → ↓LDL

PCSK9 inhibition

1 By Monoclonal Antibodies

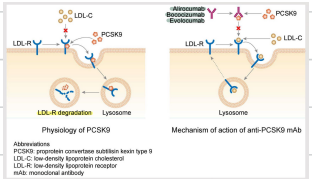
"Evaluate all bad cholesterol"

- Evolocumab
- alirocumab
- Bococizumab

PCSK9 inhibitors

Liver ↓ produce PCSK9 — binds to → LDL-R

↑LDL-C ← ∴ Degredation



* SE *

Flue like syndrome (gone within 1 week)

2 By RNA Silencing

Same target with different MOA

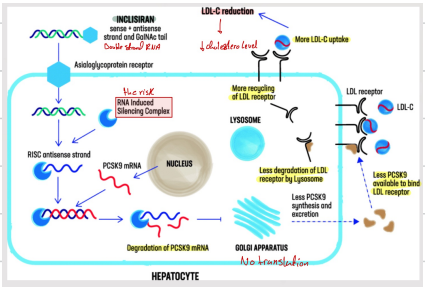
- Inclisiran → Synthetic small interfering RNA (siRNA)

↳ shows comparable effects to that of PCSK9 Monoclonal Antibodies

SEs

inclisiran vs placebo group

Higher (17%) ← injection-site reaction → Mild (1.7%)



ApoC-III inhibitor

Key regulator of TG Metabolism

Apolipoprotein C-III (apoC3)

ApoC-III protein ⊣ LPL —Degrade (X)→ Triglyceride (VLDL) & chylomicrone

combain

we ⊖ it to ↓ VLDL (TG) & chylomicrone level

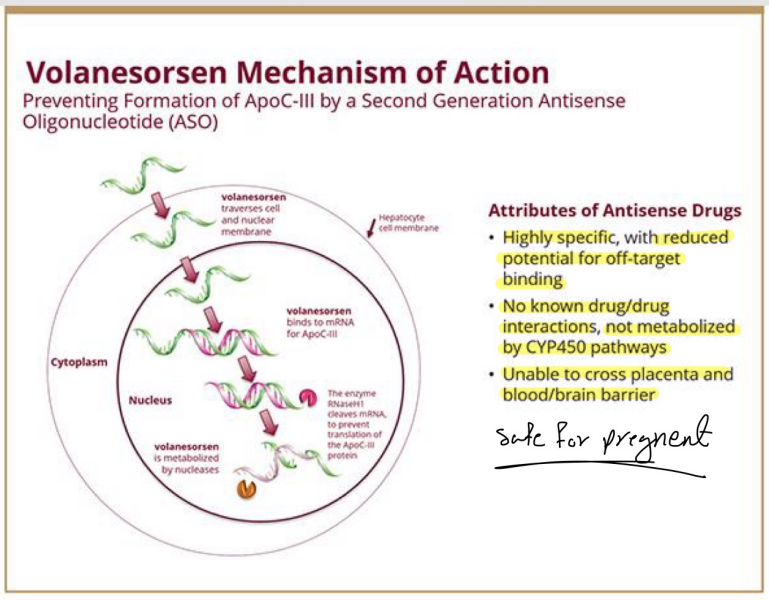
loss-of-function mutations in the APOC3 gene are associated with 40% lower plasma TG levels and a 40% lower risk of CVD
↳ if its result of VLDL

1) RNA silencing

Volanesorsen : Antisense oligonucleotide (ASO) target ApoC3 mRNA

Tested in pts with elevated TG levels & with Familial chylomicronemia syndrome (FCS)
autosomal recessive disease of chylomicron Metabolism.

* SE *
- Thrombocytopenia
&
- injection-site reactions



ANGPTL3 inhibitor

was proposed that this Blocking might produce beneficial effect on CV risk & future outcomes

ANGPTL3 ⊣ HDL-C (Degrade X) EL (endothelial lipase)

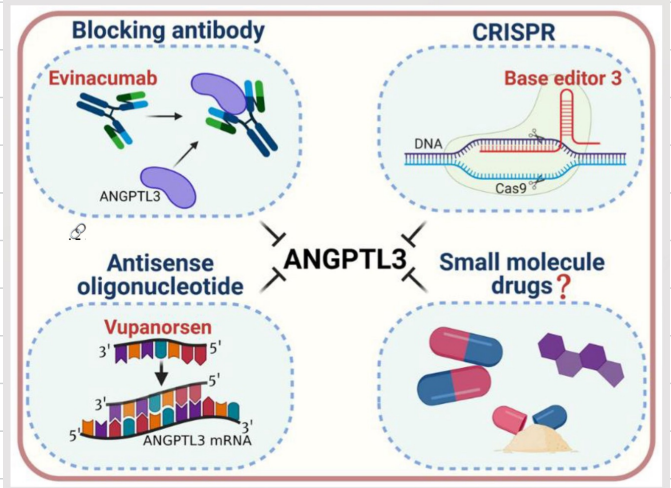
ANGPTL3 ⊣ LPL (Degrade X) → Triglyceride (VLDL) & chylomicrone

* ↓ TG, LDL-C & HDL-C independently of LDL-R function

2 Mechanisms

Monoclonal Antibody
Neutralizing levels in serum
(Evinacumab)
SE
Influenza like effect was observed in 11%

Antisense oligonucleotide
(Vupanorsen)
inhibiting production in Hepatocytes



- All drugs in this lecture (new LDL-C LOWERING AGENTS) are not considered first line therapy
- They all have activities, but we use them as Add On Drugs to Statins (and others) ,rather than being new 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 Monoclonal Antibodies	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.