PCSK9 Inhibition (mAbs and siRNA)

Key Takeaways

- The two classes of drugs that target PCSK9 are monoclonal antibodies (mAbs) and small interfering RNAs (siRNAs)
- mAbs bind directly to circulating PSCK9 proteins to prevent their interaction with LDL-C receptors, enhance the recycling of those receptors at the surface of the cells, and lead to increased clearance of LDL-C particles from circulation
- siRNA therapies utilize the RNAi pathway to inhibit the expression of specific genes. Inclisiran inhibits the production of PCSK9 proteins in the liver using this process
- Inclisiran is hepatocyte-specific as it binds to GalNAc receptors and is endocytosed where it interacts with RISC in the cytoplasm
- Phase 3 trials of inclisiran have shown an average LDL-C lowering of 51% with minimal injection site reaction as the only side effect

What is the role of PCSK9 proteins in ASCVD?

PCSK9 proteins regulate the expression of LDL receptors on hepatocytes, which are responsible for removing LDL-C from circulation.

High levels of PCSK9 → Enhanced degradation of LDL receptors = Reduced LDL clearance and elevated LDL-C levels

This contributes to the development and progression of atherosclerosis, as increased LDL-C promotes the formation of lipid-rich plaques in arterial walls.

Approaches to Targeting PCSK9

Targeting PCSK9 can effectively:

- Modulate LDL receptor expression
- Lower LDL cholesterol level
- Reduce the risk of ASCVD events in patients

Two distinct approaches to PCSK9 inhibition have revolutionized the management of hypercholesterolemia: monoclonal antibodies and siRNA.

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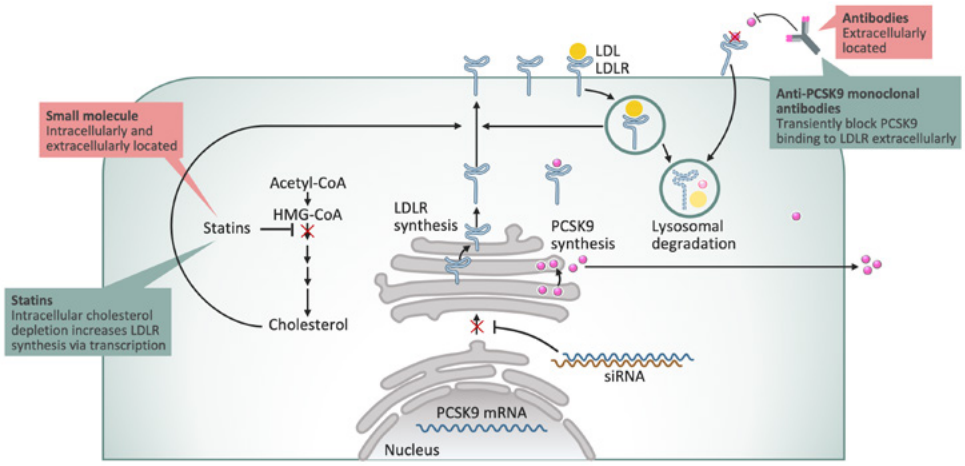
Monoclonal Antibodies: Evolocumab and Alirocumab

- Selectively bind to PCSK9 in the blood, preventing its interaction with LDL receptors on hepatocytes. This enhances the recycling of LDL receptors, leading to increased LDL clearance from circulation.
- Two drugs in this class are available in Canada: evolocumab and alirocumab
- Administered by subcutaneous injection every 2 to 4 weeks
- Access in Canada can be challenging due to reimbursement criteria*

**Please refer to the "Key Tips to Maximize Therapeutic Access for Your Patients" document*



HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; LDLR: low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; NPC1L1, Niemann-Pick C1-like protein.
Nordestgaard BG et al. Nat Rev Cardiol. 2018;15(5):261-272. 2. Katzmann JL et al. Front Physiol. 2020;11:595819.

Efficacy

- Shown to lower LDL levels by about **50 to 60%**
- Two large outcome studies have been completed with mABs:
  - FOURIER (>27,000 patients with stable cardiovascular disease) and ODYSSEY OUTCOMES (~19,000 patients with a relatively recent ACS)
  - Inclusion criteria included LDL-C levels above 1.8 mmol/L despite treatment with moderate-tohigh dose statin therapy
  - PCSK9 inhibition reduced the primary MACE plus endpoint by ~15% and reduced the traditional MACE outcome by **~20%.**

Safety

- The only notable side effect observed was a small increase in injection site reactions, which usually consisted of mild erythema or hematoma

Results of a 5-year open-label extension for FOURIER:

- After the initial ~2 years of the parent trial, all patients received open-label evolocumab for an additional 5 years
- Patients who received evolocumab during the randomized phase continued to show significant benefits in terms of the MACE-plus and traditional MACE outcomes, and they also had a significant **23% relative reduction in CV mortality**
- No loss of efficacy with regard to LDL-C lowering, and no new safety signals emerged, even in those patients who achieved LDL levels as low as 0.5 mmol/L

Dosing

- The standard dosing regimen for evolocumab is a subcutaneous injection of 140 mg every two weeks or 420 mg once monthly.
- The standard dosing regimen for alirocumab is a subcutaneous injection of 75 mg or 150 mg once every 2 weeks.

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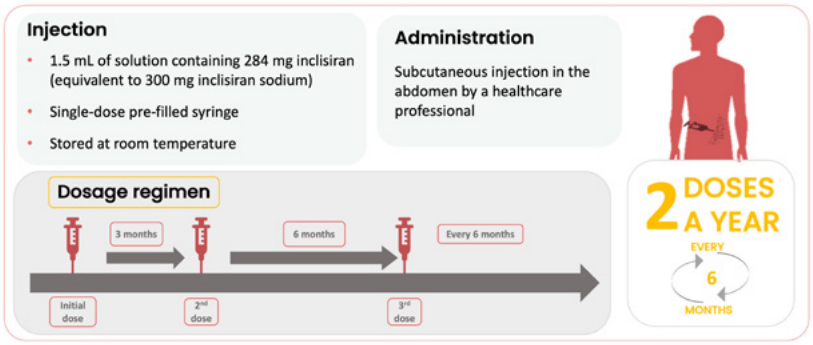
Small interfering RNA (siRNA): inclisiran

- siRNA is a class of double-stranded RNA molecules that play a crucial role in the regulation of gene expression
- siRNA therapy focuses on selectively inhibiting the expression of specific genes by using short RNA molecules to treat diseases caused by genetic abnormalities or dysregulated gene expression
- Inclisiran is the only siRNA therapy used for the treatment of hypercholesterolemia. It **targets and inhibits the production** of PCSK9 in the liver
- Inclisiran has sustained, long-term efficacy, and is administered twice a year via subcutaneous injection by a healthcare professional

Dosing

- Inclisiran is administered via subcutaneous injection by a healthcare professional (pharmacist, nurse, or physician). A single-dose pre-filled syringe contains 1.5 mL of solution containing 284 mg of inclisiran, which is equivalent to 300 mg of inclisiran sodium
- The initial dose of inclisiran is followed by a second dose after 3 months, and **additional doses every 6 months.**

Inclisiran dose and administration



- Poor adherence to currently available therapies is an important contributing factor and has been shown to be associated with an increased risk of CVD
- Inclisiran's infrequent dosing regimen may contribute to higher adherence — even complete adherence if inclisiran is administered by healthcare providers

CVD, cardiovascular disease.
Inclisiran Product Monograph, Novartis Canada. 2. Cupido AJ et al. Cardiovasc Research. 2020;116:e126-e139. doi:10.1093/cvr/cvaa.212.

Prolonged pharmacodynamic effect

- Inclisiran is cleared from the blood within about 48 hours and has prolonged action in the liver, allowing for a relatively infrequent dosing schedule
- The effects of inclisiran last 6 months
- Inclisiran has a short half-life (96 hours) and is cleared from the plasma in 24 to 48 hours
- There is no concern of long-lasting side effects and studies have not reported any such case. Additionally, studies have shown no severe adverse events associated with inclisiran

Efficacy

Patient-level, pooled analysis of ORION-9, −10 and −1 1 in patients with FH or ASCVD revealed:

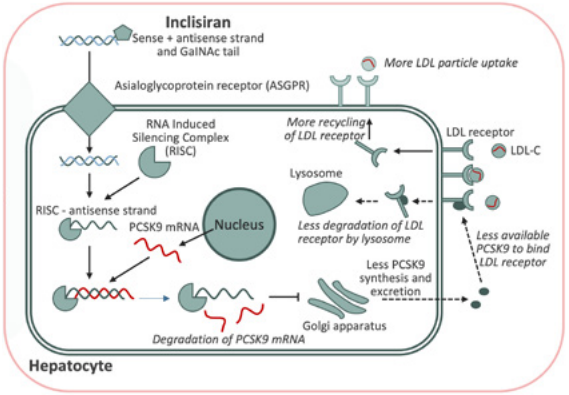
- LDL-C reduction by an average of ~51% in the inclisiran-arm
- **26% reduction in the rate of CV events***
- Consistent and persistent LDL-C reduction over 4 years in the extension study ORION-3

Safety

- The only notable side effect relative to placebo was a small increase in local injection site reactions
- Safety profile of inclisiran is similar to placebo in a high-risk population irrespective of CKD (stage 1-4), PVD, glycemic or BMI status
- Inclisiran can be used in patients with an eGFR higher than 15 mL/min. Inclisiran should not be used in patients who are on dialysis or have an eGFR less than 15 mL/min

Mechanism of action of inclisiran

- Key to safety is GalNAc conjugation
- Inclisiran binds to ASGPR conferring liver specificity
- Inclisiran plasma levels are undetectable with 48 hours



ASCVD, atherosclerotic cardiovascular disease; GalNAc, N-Acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LDLR: low-density lipoprotein receptor; mRNA: messenger ribonucleic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA: ribonucleic acid; RISC: RNA-induced silencing complex.Adapted from Nordestgaard BG et al. Nat Rev Cardiol. 2018;15(5):261-272.

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