AIM-LO: PCSK9 inhibition (mAbs and siRNA) – Dosing FAQs
Presented by Dr. Michael Heffernan

How are monoclonal antibodies (alirocumab and evolocumab) dosed?
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 two weeks. Both can be self-administered or administered by a healthcare professional.

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

The sustained duration of the effect of inclisiran is due to inclisiran's chemical modifications that increase its stability by decreasing its susceptibility to degradation from exonucleases and endonucleases. Inclisiran's sustained effects can also be attributed to the fact that a single small interfering RNA-bound RISC complex can cleave many mRNA transcripts.

Are there any drug-drug interactions with inclisiran?
According to the product monograph, inclisiran is not expected to have clinically significant interactions with other medications.

Can inclisiran be used in patients with CKD, and if so, what is the minimum safe eGFR?
Yes. A pooled subgroup analysis of the ORION-9, 10 and 11 trial showed the safety profile of inclisiran was similar to placebo in a high-risk population irrespective of CKD, PVD, glycemic or BMI status. The product monograph indicates that no dose adjustment is necessary for patients with mild to moderate renal impairment.

It can be used in patients with an eGFR higher than 15 mL/min according to the product monograph and Health Canada. Inclisiran should not be used in patients who are on dialysis or have an eGFR less than 15 mL/min.

If a patient experiences a side effect with inclisiran will it last for 6 months? What would I tell the patient?
Although the effects of inclisiran last 6 months, the drug has a short half-life (96 hours) and is cleared from the plasma in 24 to 48 hours. As such, 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.

Are siRNA therapies similar to gene therapy?
No, siRNA therapy focuses on selectively inhibiting the expression of specific genes by using short RNA molecules, while gene therapy involves introducing therapeutic genes to correct or modify the functioning of genes in the patient's cells.

The goal of siRNA therapy is to modulate the activity of specific genes to treat diseases caused by genetic abnormalities or dysregulated gene expression. The goal of gene therapy is to provide a very long-term or permanent correction of genetic defects and treat genetic disorders by altering the patient's genetic makeup. Small interfering RNA therapy is not integrated in the genome and does not alter your genetic make-up.

Now, I invite you to watch Dr. Lawrence Leiter’s video, where he discusses the efficacy and safety data on evolocumab, alirocumab, and inclisiran.