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PCSK9 Targeted Therapy to Lower Cholesterol and Reduce Cardiovascular Events

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Introduction

Cardiovascular disease (CVD) is an insidious threat that requires attention. Modifying risk factors can work toward preventing the current CVD epidemic.[1] Elevated low-density lipoprotein cholesterol (LDL-c) is a well-established and modifiable risk factor for cardiovascular, cerebrovascular, and peripheral vascular diseases. Despite receiving maximally tolerated doses of statin therapy, many Canadian patients with CVD do not achieve LDL-c targets.[2] Additional lipid-lowering therapies, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), are warranted.[3]

This paper reviews the mechanisms of action and clinical trial evidence for contemporary lipid-lowering therapies, including PCSK9 inhibitor monoclonal antibodies such as evolocumab and alirocumab, and small interfering RNA (siRNA) modulators such as inclisiran, to aid Canadian clinicians in maintaining best practices.

PCSK9 and Its Role in Lipid Metabolism

PCSK9 is secreted by hepatocytes, hindering low-density lipoprotein receptor (LDL-R) recycling and reducing LDL-R expression on the cells' surface. PCSK9 binds to the LDL-R on the hepatocytes' surface, resulting in a conformational change in the LDL-R such that it becomes trapped in the cell's endosome and cannot return to its surface. This process promotes LDL-R degradation and reduces its levels at the cell surface, leading to increased circulating LDL-c levels. Therefore, blocking PCSK9 prevents the degradation of the LDL-R, leading to increased LDL-R on the hepatocyte surface and enhanced LDL-c clearance, lowering LDL-c concentration.

Genetic studies have linked PCSK9 to individuals with hypercholesterolemia[4] and families with nonsense mutations to those with very low LDL levels.[5] These studies provided the impetus to use this protein as a therapeutic target to lower LDL-c in those with hypercholesterolemia or those with difficulties achieving therapeutic targets with traditional statin therapies.

PCSK9 Monoclonal Antibodies: Alirocumab and Evolocumab

Alirocumab (Praluent) and evolocumab (Repatha) are monoclonal antibodies that bind to extracellular PCSK9, leading to reduced degradation of LDL-R and increasing their availability for LDL-c clearance.

Clinical Efficacy

The efficacy and safety of alirocumab on LDL-c was initially assessed in the ODYSSEY LONG TERM trial, a randomized trial involving 2341 patients at high-risk for cardiovascular events with LDL-c levels >1.8 mmol/L despite receiving the maximally tolerated doses of statin therapy.[6] Patients were eligible if they were 18 years of age or older with heterozygous familial hypercholesterolemia or established coronary disease or its equivalent. The majority of patients were men, with an average age of 60, with 68.9% having a history of coronary heart disease. Some patients had familial hypercholesterolemia (17.7%). The baseline LDL-c level at entry was 3.2 mmol/L. Patients received either alirocumab 150 mg or placebo every 2 weeks for 78 weeks. By 24 weeks, the mean LDL-c level was reduced by −61.9%±1.3% ($p<0.001$) and was maintained for the duration of the 78 weeks of the study (−56.0%±1.6% reduction). The study drug resulted in more adverse side effects, including

injection site reactions (5.9% alirocumab vs 4.2% placebo), myalgias (5.4% alirocumab vs 2.9% placebo), neurocognitive events (1.2% alirocumab vs
0.5% placebo) and ophthalmologic events (2.9% alirocumab vs 1.9% placebo). A specific safety analysis of the larger ODYSSEY OUTCOMES trial demonstrated alirocumab's safety profile among higher-risk individuals[7] and did not confirm adverse side effects. Alirocumab was deemed safe except for a slight increase in the risk of injection site reactions.

The efficacy of evolocumab on LDL-c was assessed In the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) in adult patients with LDL-c levels >1.94 mmol/L and fasting triglyceride levels <4.52 mmol/L. Patients were stratified to diet alone or diet plus lipid-lowering therapy baselines and then received either evolocumab or placebo. A total of 901 patients with hyperlipidemia received evolocumab over 1 year. The mean reduction in LDL-c from baseline was 57.0±2.1% (p<0.001).[8]

Outcome Trials

The ODYSSEY OUTCOMES trial was a randomized, double-blind, trial involving 18,924 post-acute coronary syndrome (ACS) patients on evidence-based statin therapy, comparing the addition of alirocumab to placebo adequately powered for clinical outcomes.[9] The trial primarily enrolled white men with a history of hypertension following ACS, with 48% having NSTEMI or 34.9% having STEMI. The primary endpoint, a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization, was reduced in the alirocumab group (9.5%) vs the placebo group (11.1%), with a hazard ratio (HR) of 0.85 (95% confidence interval [CI] 0.78–0.93, p<0.001). The secondary end-points of death/myocardial infarction/ischemic stroke were reduced in the alirocumab group vs. placebo group (10.3% vs. 11.9%, p=0.0003), all-cause mortality was reduced (3.5% vs. 4.1%, p=0.026), and ischemia-driven revascularization was reduced (7.7% vs. 8.8%, p=0.009). There was an increase in mild, self-limiting injection site reactions of 3.8% in the alirocumab group vs 2.1% in placebo.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study was a randomized, double-blind, placebo-controlled trial of 27,564 patients comparing evolocumab to placebo in those 40-85 years of age with cardiovascular disease or at risk of cardiovascular disease with an LDL-c level >1.8 mmol/L while on statin therapy.[9] The majority of patients were male (75%) with a previous myocardial infarction (80.9%) on high-intensity statin therapy (69.5%) with a baseline LDL-c level of 2.38 mmol/L. Patients received subcutaneous injections of evolocumab 140 mg every 2 weeks or 420 mg subcutaneous every month, with the dose increased to 420 mg every 2 weeks if additional LDL-c lowering was required. The primary endpoint, which included a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization, was reduced in patients in the evolocumab group compared to the control group (9.8% vs 11.3%; HR 0.85; 95% CI 0.79–0.92; p<0.001). The secondary endpoint, which included a composite of cardiovascular death, myocardial infarction or stroke, was also reduced in the evolocumab group compared to placebo (5.9% vs 7.4%, HR 0.80; 95% CI 0.73–0.88; p<0.001). There was an increase in mild injection-site-related reactions (2.1% in the evolocumab group vs 1.6% of those receiving placebo). There was a reduction in ischemic stroke in the evolocumab group vs the placebo group 1.2% versus 1.6% (HR 0.75; 95% CI 0.62–0.92; p=0.005).[10] Importantly, in the 13.2% of patients with peripheral arterial disease (PAD), there was a reduced risk of major adverse limb events (HR 0.58; 95% CI 0.38–0.88; p=0.0093),[11] highlighting the benefit of aggressive LDL lowering for these patients.[12]

In an open-label extension trial that followed patients for a median of 5 years, those treated with evolocumab experienced a 15% lower risk of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization (HR 0.85; 95% CI 0.75–0.96; p=0.008).[13] In addition, there was a 20% lower risk of CV death, myocardial infarction, or stroke (HR 0.80; 95% CI 0.68–0.93; p=0.003) and a 23% lower risk of cardiovascular death (HR 0.77; 95% CI 0.60–0.99; p=0.04). Compared with patients originally randomized to placebo, patients who received evolocumab had fewer cardiovascular events and lower cardiovascular mortality an important signal in the long-terms outcomes of PCSK9 inhibitor-treated patients.

Indications For Use in Canada

Alirocumab was approved on July 31, 2019, for use in combination with the maximum tolerated dose of a statin to reduce the risk of myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. It is also indicated to be used alone or with other lipid-lowering therapies in patients with heterozygous familial hypercholesterolemia.[14]

Evolocumab was approved in Canada on September 15, 2015, for the reduction of elevated LDL-c in adults with heterozygous familial hypercholesterolemia or ASCVD, with or without other lipid-lowering therapies in patients who require additional lowering of LDL-c, either alone or in combination with non-statin therapies for whom statins are contraindicated.[15]

PCSK9 siRNA: Inclisiran

Mechanism of Action

Inclisiran is a long-acting, small interfering RNA (siRNA) that selectively silences the translation of PCSK9 mRNA in the liver to reduce the production of PCSK9 protein. This results in an increased availability of the LDL-R on hepatocytes, leading to increased clearance of LDL-c. Due to its mechanism of action interfering with mRNA production of PCSK9 in the liver, inclisiran can be given every 6 months subcutaneously after the initial dose and 3-month second dose.

Clinical Efficacy

The ORION-9 (Trial to Evaluate the Effect of Inclisiran Treatment on Low-Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease), ORION-10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol), and ORION-11 (Inclisiran for Subjects

Study Drug	Mechanism of Action	LDL-c Lowering	Clinical Efficacy
Alirocumab	Antibody to PCSK9	−61.9±1.3%	**Patients studied:** Post-acute coronary syndrome patients on maximally tolerated statin therapy. **Outcome:** Reduction in a composite of coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization.
Evolocumab	Antibody to PCSK9	−57.0±2.1%	**Patients studied:** Patients with cardiovascular disease or at risk with an LDLc level >1.8 mmol/L on maximally tolerated statin therapy. **Outcome:** Reduction in a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization.
Incilisiran	siRNA to PSCK9	ORION- 9: −47.9%±5.6% ORION-10: −53.8%±2.8% ORION-11: 49.2%±2.4%	Pending Ongoing CVO trials, – Pooled analysis is encouraging

Table 1. PCSK9 targeted therapies, efficacy and indications.; *courtesy of Beth L. Abramson, MD, FRCPC, FACC, Seana ML. Nelson, MD, FRCPC*

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; **CVO:** cardiovascular outcome trials; **LDL-c:** low-density lipoprotein cholesterol; **PCSK9:** proprotein convertase subtilisin/kexin type 9

With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol) studies investigated the LDL-c lowering capabilities of inclisiran. These trials demonstrated an approximate 50.3% reduction in LDL-c levels.[16,17] Injection site reactions were more frequent in the study group, and most of them were mild.

The ORION-9 study included individuals with familial hypercholesterolemia who had LDL-c levels >2.6 mmol/L despite receiving maximally tolerated statin therapy with or without ezetimibe.[16] Patients were randomized to receive either inclisiran 284 mg or placebo. The primary endpoints included the percentage change in LDL-c levels from baseline to day 510. In the inclisiran group, LDL-c levels were reduced by 39.7% (95% CI −43.7 to −35.7) and were increased by 8.2% (95% CI 4.3–12.2) in the placebo group, resulting in a net change of −47.9 percentage points (95% CI −53.5 to −42.3; p<0.001). Other outcomes included lower levels of total cholesterol, non-HDL, apolipoprotein B, and triglycerides compared to the placebo group. In addition, lipoprotein (a) was reduced by 17.2% compared to baseline.

The ORION-10 study included patients in the US with atherosclerotic cardiovascular disease and LDL-c levels >1.8 mmol/L on a background of lipid-lowering therapies.[17] The ORION-11 study included individuals from South Africa and Europe with atherosclerotic cardiovascular disease and LDL-c levels >1.8 mmol/L? or an atherosclerotic disease equivalent.[17] Individuals received either inclisiran 284 mg or placebo. In the ORION-10 study, the coprimary endpoints included the percentage LDL-c change, which was 1% in the placebo group and 51.3% in the inclisiran group, resulting in an absolute inter-group change of -53.8% (95%CI −55.7 to −48.8; p<0.001). In the ORION-11 study, LDL-c levels increased by 4% in the placebo group and decreased by 45.8% in the inclisiran group, leading to an in-between difference of -49% (95% CI −53.1 to −46.6; p<0.001).

The ORION-3 trial, a 4-year open-label extension study of 382 patients previously enrolled in the ORION-1 study, demonstrated the safety and efficacy of inclisiran.[18] Patients who received inclisiran in the ORION-1 trial received 284 mg biannually. Those randomized to the placebo group in the ORION-1 trial received 140 mg of evolocumab subcutaneously and then transitioned to 284 mg of inclisiran after 1 year for the remainder of the study. The mean percentage reduction in LDL-c levels ranged from −34·3% to −53·8%, and the mean absolute change in LDL-c concentrations ranged from−1·13 mmol/L to −1·76 mmol/L. The most common treatment-related event was nasopharyngitis in the inclisiran-only group (19%) and hypertension (20%) in the switching group. Between 25-28% of patients in the study experienced injection site-related reactions.

Outcome Data

The effect of inclisiran on cardiovascular morbidity and mortality has not been assessed in a specific trial, but pooled data from the three Phase III trials is encouraging.[19] The ORION-4 trial, which has enrolled 16,124 participants with pre-existing atherosclerotic disease, aims to determine if inclisiran can reduce major cardiac events [ClinicalTrials.gov Identifier: NCT03705234] and expects to report findings in 2026. The VICTORION-1P and 2P trials will assess the efficacy of inclisiran in approximately 15,000 patients who are either at high risk for primary prevention or have established cardiovascular disease. The findings are expected to be reported in 2029 and 2027, respectively.

Indications For Use In Canada

Inclisiran (Leqvio) was approved in Canada on July 23, 2021, to further reduce LDL-c levels in adults on maximally tolerated statin therapy who have heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with atherosclerotic cardiovascular disease.[20]

Conclusions

PCSK9 plays an important role in handling LDL-R and, therefore, circulating LDL-c. Mendelian studies have demonstrated a correlation between PCSK9 overexpression and increased cardiovascular disease, while nonsense mutations are associated with a lower cardiovascular risk.

The Canadian Cardiology Society 2021 Dyslipidemia Guidelines endorse PSCK9i for familial and ASCVD patients. In those with familial hypercholesterolemia (FH) or genetic dyslipidemia, PSCK9i is indicated if LDL >2.5, ApoB >0.85, or non-HDL-c >3.2. For ASCVD patients with LDL-c >2.2 mmol/L, non-HDL-c >2.9 mmol/L, or ApoB >0.8 g/L despite max statin therapy, PSCK9i is recommended as an add-on, especially for high PSCK9i benefit patients, including those with acute coronary syndrome (ACS) in the past year or additional risk factors like recurrent ACS, past CABG, poly-vascular disease, symptomatic PAD,

high LDL-c, heterozygous FH, elevated Lp(a), or diabetes. If ASCVD patients don't meet these criteria but have LDL-c >1.8 mmol/L, ApoB >0.7 g/L, or non-HDL >2.4 on maximum statin therapy, ezetimibe is added first, with PSCK9i considered later. Both PCSK9 inhibitors, evolocumab and alirocumab, reduced cardiovascular and stroke events. In addition, PCSK9 modulation with inclisiran also effectively lowers LDL-c, with cardiovascular outcome trial data pending. Overall, PCSK9 targeted therapies provide therapeutic options to lower LDL-c to levels that were not possible several decades ago. Intensification of lipid-lowering in our at-risk patients will help reduce the tremendous burden cardiovascular disease places on our healthcare system and improve the health of our patients.[21]

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