Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors

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1 Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are a new class of low-density lipoprotein (LDL-C)–lowering medications

PCSK9 is a protease that degrades hepatic LDL-C receptors. Evolocumab and alirocumab are fully human monoclonal antibodies administered as subcutaneous injections that inhibit PCSK9, preserving receptor availability to clear circulating LDL-C.[1,2]

2 PCSK9 inhibitors have been shown to improve cardiovascular outcomes

In randomized, placebo-controlled trials of patients with atherosclerotic cardiovascular disease and LDL-C ≥ 1.8 mmol/L despite maximal statin therapy with or without ezetimibe, evolocumab and alirocumab both reduced major cardiovascular events with an absolute risk reduction of 1.5% (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.79–0.92, $p < 0.001$; number needed to treat: 67) after 2.2 years of follow-up and 1.6% (HR 0.85, 95% CI 0.78–0.93, $p < 0.001$; number needed to treat: 63) after 2.8 years of follow-up, respectively.[1,2] These benefits were driven primarily by reduced morbidity.

3 PCSK9 inhibitors are recommended as add-on therapy in patients at very high risk

The 2018 American dyslipidemia guideline recommends adding PCSK9 inhibitors in patients at very high risk (multiple cardiovascular events or 1 cardiovascular event plus risk factors) with LDL-C ≥ 1.8 mmol/L despite maximal statin therapy with or without ezetimibe.[3] PCSK9 inhibitors are also recommended in patients with severe hypercholesterolemia (LDL-C ≥ 4.9 mmol/L) above target despite maximal statin therapy and ezetimibe.[3]

4 PCSK9 inhibitors are well tolerated, but long-term safety data are lacking

Mild, self-limiting injection-site reactions are the most common adverse effect; no clinically important drug interactions have been reported.[1,2]

5 The price of PCSK9 inhibitors limits their cost-effectiveness

Economic evaluations of evolocumab and alirocumab incorporating data on clinical outcomes[1,2] conclude that these medications are not cost-effective at current pricing, even with a $100 000 threshold quality-adjusted life-year cost.[3–5] Their annual cost is more than $15 000 in the United States and approximately $7500 in Canada.[4,5] Substantial price reductions (e.g., to about $2000/yr) are needed in order for them to be cost-effective.[4,5] Provincial coverage varies and is generally limited to patients at high risk.

References

1. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22.
2. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097-107.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines [published erratum in Circulation 2019;139:e1182-6]. *Circulation* 2019;139:e1082-143.
4. Kazi DS, Penko J, Coxson PG, et al. Cost-effectiveness of alirocumab: a just-in-time analysis based on the ODYSSEY outcomes trial. *Ann Intern Med* 20192019;170:221-9.
5. Lee TC, Kaouache M, Grover SA. Evaluation of the cost-effectiveness of evolocumab in the FOURIER study: a Canadian analysis. *CMAJ Open* 2018;6:E162-7.

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