

Do PCSK9 inhibitors reduce cardiovascular events?

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Clinical question

Do proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors decrease cardiovascular disease (CVD) events. If so, are they cost-effective?

Bottom line

For patients with CVD taking maximally tolerated statins, adding evolocumab or alirocumab decreases new CVD events for an additional 1 in 65 patients compared with placebo over about 2.5 years. Routine use of these agents is not currently cost-effective.

Evidence

- Two large industry-sponsored, placebo-controlled trials evaluated clinical outcomes. Patients had existing CVD and a low-density lipoprotein (LDL) level of 1.8 mmol/L or greater while taking maximally tolerated statins.^{1,2}
 - A study randomized 27 564 patients to evolocumab (140 mg every 2 weeks or 420 mg/month) or placebo.¹ At 2.2 years, the reduction in new CVD events (evolocumab 9.8%, placebo 11.3%) was statistically significant (number needed to treat [NNT]=67) independent of the baseline LDL level; there was no difference in death by any cause.
 - A study pending publication randomized 18 924 patients after acute coronary syndrome to alirocumab (75 to 150 mg every 2 weeks) or placebo.² At 2.8 years, there was a statistically significant reduction in new CVD events (9.5% for alirocumab and 11.1% for placebo, NNT=63) and death by any cause (alirocumab 3.5%, placebo 4.1%; 6 fewer deaths; NNT=167).
 - Adverse events were primarily injection site reactions (number needed to harm of about 100).^{1,2}
- Other smaller RCTs were limited by only reporting surrogate outcomes,³ lack of blinding,^{4,5} and enrolling familial hypercholesterolemia patients⁴ or patients from previous studies,^{3,5} and found inconsistent effects on CVD.^{5,6}

Context

- Bococizumab research stopped owing to development of drug-neutralizing antibodies.⁷
 - Developing neutralizing antibodies to alirocumab or evolocumab is rare and usually clinically insignificant.^{1,8}
- No studies on statin-intolerant patients evaluated clinical outcomes.⁹

- Some guidelines recommend PCSK9 inhibitors for patients with familial hypercholesterolemia or CVD whose LDL levels are above “target” despite taking a maximum-tolerated statin with or without ezetimibe.¹⁰
- Routine use of PCSK9 inhibitors is not cost-effective at current Canadian prices (about \$7100 per year).¹¹

Implementation

Statins are first-line lipid-lowering therapy, as they have the best CVD risk reduction.¹² Statin-associated muscle symptoms (SAMS) occur in 1% to 5% of users in trials and are dose-related.¹² Statin discontinuation is associated with increased risk of death and CVD events.¹³ Most patients who report SAMS tolerate restarting statins at lower or alternate-day doses of the same or a different statin.¹² Statin rechallenge should be attempted before using ezetimibe or PCSK9 inhibitors. Coenzyme Q10 does not prevent or alleviate SAMS beyond placebo.¹⁴

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Competing interests
None declared

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