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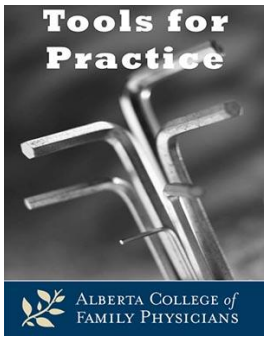

PCSK9 Inhibitors: Cardiovascular prevention panacea or pesky, pricey pokes?

Clinical Question: Do pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease cardiovascular events, and if so, are they cost-effective?

Bottom Line: For patients with cardiovascular disease (CVD) already on maximally tolerated statins, adding evolocumab or alirocumab decreases new CVD events for an additional one in 65 patients compared to placebo over ~2.5 years. Routine use of these agents is not cost-effective at current prices.

Evidence:

- Focusing on two largest, industry-sponsored, placebo-controlled trials evaluating clinical outcomes.[1,2] Patients had existing CVD and LDL ≥1.8 mmol/L while on maximally tolerated statins.[1,2]
  - Evolocumab: 27,564 patients randomized to evolocumab (140 mg every two weeks or 420 mg monthly) or placebo.[1] At 2.2 years:
    - New CVD events: Evolocumab 9.8%, placebo 11.3%, statistically significant.
      - Number Needed to Treat (NNT)=67.
      - CVD reduction: Independent of baseline LDL.
    - Death (any cause): No difference.
  - Alirocumab: (pending publication) 18,924 patients post-acute coronary syndrome randomized to alirocumab (75-150 mg every two weeks) or placebo.[2] At 2.8 years statistically significant reduction in:
    - New CVD events: Alirocumab 9.5%, placebo 11.1%, NNT=63.
    - Death (any cause): Alirocumab 3.5%, placebo 4.1%, NNT=167.
      - Note: Statistical difference in death based on six fewer deaths.
- Adverse events:[1,2]
  - Primarily injection site reactions: Number Needed to Harm ~100.
- Other smaller randomized controlled trials limited by only reporting surrogate outcomes,[3] lack of blinding,[4,5] and enrolling familial hypercholesterolemia patients[4] or patients from previous studies.[3,5] These studies found inconsistent effects on CVD.[5,6]

Context:

- Bococizumab research and development stopped due to development of drug-

neutralizing antibodies.[7]
    - Development of neutralizing antibodies to alirocumab and evolocumab is rare and usually clinically insignificant.[1,8]
- No studies on statin intolerant patients have evaluated clinical outcomes.[9]
- Some guidelines recommend considering PCSK9 inhibitors for patients with familial hypercholesterolemia or CVD whose LDL remains above 'target' despite maximum-tolerated statin +/- ezetimibe.[10,11]
- Routine use of PCSK9 inhibitors in CVD patients is not cost-effective at current Canadian prices (~$7,100/year).[12] A >90% price reduction would be required for cost-effectiveness.[12]

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Authors do not have any conflicts of interest to declare.

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