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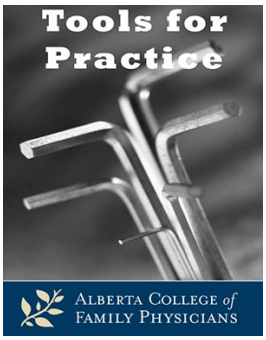
Reviewed: February 15, 2017
Evidence Updated: Slight change to context regarding insurance coverage
Bottom Line: No Change
First Published: February 6, 2017



GLP-1 Analogues in Diabetes: As sweet as can be?

Clinical Question: Do glucagon-like peptide 1 analogues (GLP-1) improve patient-oriented outcomes in type 2 diabetes?

Bottom Line: Compared to placebo, semaglutide and liraglutide, but not lixisenatide, reduce cardiovascular disease (CVD) for ~1 in 50 diabetics with existing CVD over 2-4 years, irrespective of specific A1c targets (attaining ~7.5%). These drugs reduce weight 0.7-4.3 kg, but around one in 25 more than placebo will stop due to gastrointestinal effects. Some uncertainty around neoplasm risk remains.

Evidence:
Three randomized controlled trials (RCTs), mean age 60-65, diabetic 9-14 years, >80% past CVD. All GLP-1 subcutaneous versus placebo. Statistically significant results:

- Liraglutide (1.8 mg daily): 9,340 patients x 3.8 years:[1]
  - A1c from 8.7% to: ~7.7% liraglutude versus 8.1% placebo.
  - CVD: 13% versus 14.9%, Number Needed to Treat (NNT)=53.
  - Mortality: NNT=72.
  - Harms: Gallbladder disease, Number Needed to Harm (NNH)=83.
- Semaglutide (0.5 or 1 mg weekly; pooled): 3,297 patients x 2.1 years:[2]
  - A1c from 8.7% to: 7.3-7.6% semaglutide versus 8.3% placebo.
  - CVD: 6.6% versus 8.9%, NNT=44.
  - Mortality: No difference.
  - Harms: Retinopathy, NNH=83.
- Lixisenatide (20 mcg daily): 6,068 patients x 2.1 years:[3]
  - A1c from 7.6% to: ~7.3% lixisenatide versus ~7.6% placebo.
  - CVD or mortality: No difference.
- Other findings: Weight loss (0.7-4.3 kg), reduced nephropathy (NNT=67-98; not lixisenatide), hypoglycemia no different or lower.
  - More discontinued due to gastrointestinal irritation (NNH=16-33).

- Neoplasm (benign/malignant) numerically higher with GLP-1 agonist in each study.[1-3]
  - Meta-analyses (missing above liraglutide and semaglutide RCTs): No cancer risk.[4,5]
    - Except high-quality liraglutide RCTs, odds ratio=2.60 (1.08-6.27).[5]
  - BMJ investigation questioned whether safety adequately evaluated.[6]
  - 2014 FDA/EMA review "had not reached a final conclusion" on causality between incretins and (specifically) pancreatic cancer, despite indicating concerns were not consistent with evidence.[7]

Context:

- Clinicians should prioritize patient-oriented outcomes (like CVD) rather than sugars or microalbuminuria.
- Large RCTs of DPP-4 medications demonstrate no effect on CVD and minimal to no effect on microvascular outcomes.[8]
- Liraglutide is the only GLP-1 agonist available in Canada with a large CVD trial (others: dulaglutide and exenatide), costs ~$185/month and while often covered by private insurance, it is not covered by public insurance plans outside of Quebec.

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Disclosure:
Authors have no conflicts of interest to declare.

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