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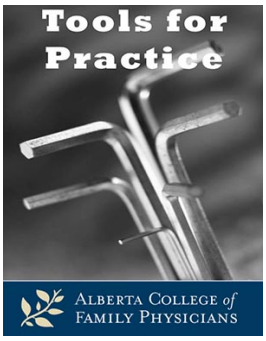

GLP-1 Analogues in Diabetes: As sweet as can be?

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 [liraglutide less severe hypoglycemia (NNT=112)], 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.
- Meta-analysis of small short trials can be misleading compared to large RCTs designed to assess patient-oriented outcomes.
  - Example: An early meta-analysis of 53 DPP-4 trials suggested a reduction in CVD,[8] but subsequent large trials showed no effect.[9]
- Liraglutide is the only GLP-1 agonist available in Canada with a large CVD trial (others: dulaglutide and exenatide), costs ~$185/month and is usually not covered by insurance plans.

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Authors have no conflicts of interest to declare.

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