Glucagonlike peptide 1 analogs in diabetes care

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Clinical question

Do glucagonlike peptide 1 (GLP1) analogs improve patient outcomes in type 2 diabetes?

Bottom line

Compared with placebo, semaglutide and liraglutide, but not lixisenatide, reduce cardiovascular disease (CVD) for about 1 in 50 patients with diabetes with existing CVD over 2 to 4 years, irrespective of specific hemoglobin A_{1c} (HbA_{1c}) targets. They reduce weight, but about 1 in 25 more patients than in the placebo group stopped treatment owing to gastrointestinal effects. Some uncertainty around neoplasm risk remains.

Evidence

Evidence from 3 RCTs (mean age 60 to 65, diabetes for 9 to 14 years, >80% had past CVD, all GLP1 analogs given subcutaneously vs placebo) was statistically significant.

- An RCT of liraglutide (1.8 mg/d) followed 9340 patients for 3.8 years[1]:
  -Initial HbA_{1c} level of 8.7% decreased to about 7.7% for liraglutide versus 8.1% for placebo.
  -Rate of CVD was 13% versus 14.9% (number needed to treat [NNT] = 53); NNT = 72 for mortality; and harms included gallbladder disease (number needed to harm [NNH] = 83).
- An RCT of semaglutide (0.5 or 1 mg/wk; pooled data) followed 3297 patients for 2.1 years[2]:
  -Initial HbA_{1c} level of 8.7% decreased to 7.3% to 7.6% for semaglutide versus 8.3% for placebo.
  -Rate of CVD was 6.6% versus 8.9% (NNT=44); no difference in mortality; and harms were retinopathy (NNH=83).
- An RCT of lixisenatide (20 µg/d) followed 6068 patients for 2.1 years[3]:
  -Initial HbA_{1c} level of 7.6% decreased to about 7.3% for lixisenatide versus about 7.6% for placebo.
  -No difference in CVD or mortality.
- Other findings were weight loss (0.7 to 4.3 kg) and reduced nephropathy (NNT=67 to 98; not with lixisenatide). Hypoglycemia was no different or slightly lower.
  -Patients often discontinued treatment owing to gastrointestinal irritation (NNH=16 to 33).
- Neoplasms were numerically higher with GLP1 use.[1-3]
  -Some meta-analyses found no cancer risk.[4,5] When only the highest-quality liraglutide RCTs were analyzed, the risk increased (odds ratio=2.60, 95% CI 1.08 to 6.27).[5]
  -Safety might not have been properly evaluated.[6]
  -A 2014 review did not reach a "final conclusion" on causality between incretins and pancreatic cancer, despite stating concerns were not consistent with evidence.[7]

Context

- Clinicians should prioritize patient-oriented outcomes (eg, CVD) rather than glucose levels or microalbuminuria.
- Large RCTs of dipeptidyl peptidase 4 inhibitors demonstrate no effect on CVD and minimal to no effect on microvascular outcomes.[8]
- Liraglutide is the only GLP1 analog available in Canada with evidence from a large CVD trial. It costs about $185 per month; it is often covered by private insurance, but it is not covered by public insurance outside of Quebec.

Implementation

Liraglutide and semaglutide (but not lixisenatide)[1-3] join empagliflozin[9] as second-line glucose-lowering agents with evidence of modest CVD risk reduction. Of note, these trials enrolled patients with very high CVD risk. The NNT in lower-risk diabetes patients would be less impressive. When additional glucose lowering is desired, it is reasonable to add liraglutide or semaglutide to metformin when the higher cost, need for injection, and potential for nausea do not dissuade the patient. Weight loss is modest, but variable and not sustained on discontinuation.[10]

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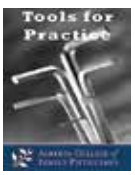
Competing interests
None declared

References

1. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375(4):311-22.
2. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375(19):1834-44.
3. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373(23):2247-57.
4. Chen H, Zhou X, Chen T, Liu B, Jin W, Gu H, et al. Incretin-based therapy and risk of pancreatic cancer in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Diabetes Ther* 2016;7(4):725-42.
5. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012;98(2):271-84.
6. Cohen D. Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed? *BMJ* 2013;346:f3680.
7. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med* 2014;370(9):794-7. Erratum in: *N Engl J Med* 2014;370(23):2253.
8. Barry A, Allan GM. *DPP-4 inhibitors: protecting your sweet heart?* Edmonton, AB: Tools for Practice; 2015.
9. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117-28.
10. Antony N, Korownyk C. *Liraglutide: weighing the evidence for weight loss*? Edmonton, AB: Tools for Practice; 2016.



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