## Diabetic retinopathy: Screening, prevention, and treatment

**In Reply:** We thank Ashley Lim for the comments on our review article. We are pleased that readers are interested in our review and appreciate the opportunity to discuss any concerns raised in the letter.

We agree that new therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 inhibitors have significant value in achieving glycemic control to prevent diabetic retinopathy, and that GLP-1 receptor agonists have complex and unclear effects on the risk for diabetic retinopathy. Yet, several studies reported findings showing that sodium-glucose cotransporter 2 inhibitors are either not associated with a significantly increased risk of diabetic retinopathy or may even be linked to a significantly reduced risk, findings that seem to support their safety.<sup>2-6</sup>

However, as we discuss in the "Glucagon-like peptide-1 receptor agonists, rapid HbA1c reduction, and retinopathy" section of our review, there

is mixed evidence on the effect of GLP-1 receptor agonists on the risk of diabetic retinopathy, with some meta-analyses and trials reporting an increased risk<sup>7-13</sup> and others reporting no significant association between GLP-1 receptor agonists and risk for diabetic retinopathy or diabetic retinopathy progression. Consistent with the fi ndings of Wai et al, 19 the stud-ies cited in our review that reported an increased risk of diabetic retinopathy observed an early rise in risk from 3 months to 3 years after patients started a GLP-1 receptor agonist. 11

Because of the mixed results in the literature, further investigations on treatment methods that can drastically reduce hemoglobin A1c, such as specifi c types of GLP-1 receptor agonists, other pharmacologic therapies, and bariatric surgery, are necessary to elucidate the mechanism of potential early worsening of diabetic retinopathy and safe management of this complication of diabetes.

In clinical practice, it is important for clinicians to follow the American Diabetes Association screening recommendations<sup>20</sup> for diabetic retinopathy and to consider referring patients to an ophthalmologist to assess retinopathy status when prescribing GLP-1 receptor agonists.

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## REFERENCES

- Chong DD, Das N, Singh RP. Diabetic retinopathy: screening, prevention, and treatment. Clev Clin J Med 2024; 91(8):503–510. doi:10.3949/ccjm.91a.24028
- 2 Tang H, Li G, Zhao Y, et al. Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: a network meta-analysis. Diabetes Obes Metab 2018; 20(5):1262–1279. doi:10.1111/dom.13232
- Ott C, Jumar A, Striepe K, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol 2017; 16(1):26. doi:10.1186/s12933-017-0510-1
- 4. Yen FS, Wei JC, Yu TS, Hung YT, Hsu CC, Hwu CM. Sodium-glucose cotransporter 2 inhibitors and risk of retinopathy in patients with type 2 diabetes. JAMA Netw Open 2023; 6(12):e2348431. doi:10.1001/jamanetworkopen.2023.48431
- Inzucchi SE, Wanner C, Hehnke U, et al. Retinopathy outcomes with empagliflozin versus placebo in the EMPA-REG OUTCOME trial. Diabetes Care 2019; 42(4):e53–e55. doi:10.2337/dc18-1355
- 6. Li C, Zhou Z, Neuen BL, et al. Sodium-glucose co-transporter-2 inhibition and ocular outcomes in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2021; 23(1):252–257. doi:10.1111/dom.14197
- Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375(19):1834–1844. doi:10.1056/NEJMoa1607141
- Wang F, Mao Y, Wang H, Liu Y, Huang P. Semaglutide and diabetic retinopathy risk in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Clin Drug Investig 2022; 42(1):17–28. doi:10.1007/s40261-021-01110-w
- Albert SG, Wood EM, Ahir V. Glucagon-like peptide 1-receptor agonists and A1c: good for the heart but less so for the eyes? Diabetes Metab Syndr 2023; 17(1):102696. doi:10.1016/j.dsx.2022.102696
- Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020; 173(4): 278–286. doi:10.7326/M20-0864
- Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA1c change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. Diabetes Care 2021; 44(1):290–296. doi:10.2337/dc20-1815

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- Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019; 381(9):841–851. doi:10.1056/NEJMoa1901118
- 13. Yoshida Y, Joshi P, Barri S, et al. Progression of retinopathy with glucagon-like peptide-1 receptor agonists with cardiovascular benefits in type 2 diabetes—a systematic review and meta-analysis. J Diabetes Complications 2022; 36(8):108255. doi:10.1016/j.jdiacomp.2022.108255
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4):311–322. doi:10.1056/NEJMoa1603827
- Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL Trial. Diabetes Care 2020; 43(2):446–452. doi:10.2337/dc19-1065
- 16. Wei J, Yang B, Wang R, et al. Risk of stroke and retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: an eight RCTs meta-analysis. Front Endocrinol (Lausanne) 2022; 13:1007980. doi:10.3389/fendo.2022.1007980
- 17. Zhang X, Shao F, Zhu L, Ze Y, Zhu D, Bi Y. Cardiovascular and microvascular outcomes of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled cardiovascular outcome trials with trial sequential analysis. BMC Pharmacol Toxicol 2018; 19(1):58. doi:10.1186/s40360-018-0246-x
- Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394(10193): 121–130. doi:10.1016/S0140-6736(19)31149-3
- Wai KM, Mishra K, Koo E, et al. Impact of GLP-1 agonists and SGLT-2 inhibitors on diabetic retinopathy progression: an aggregated electronic health record data study. Am J Ophthalmol 2024; 265:39-47. doi:10.1016/j.ajo.2024.04.010
- American Diabetes Association Professional Practice Committee.
  Retinopathy, neuropathy, and foot care: standards of care in diabetes—2024. Diabetes Care 2024; 47(suppl 1):S231–S243. doi:10.2337/dc24-S012

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