



GLP-1 receptor agonists and diabetic retinopathy

An unexpected safety signal emerged from the SUSTAIN 6 cardiovascular outcomes trial of the glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide, whereby increased rates of diabetic retinopathy were observed in trial participants randomised to semaglutide. This finding has, justifiably, led to a great deal of investigation and caution. This At a glance factsheet outlines the evidence regarding diabetic retinopathy in users of the GLP-1 RA class as a whole, and provides recommendations on safe use.

Initial safety concern

In the SUSTAIN 6 cardiovascular outcomes trial of semaglutide, diabetic retinopathy endpoints were reported in significantly more individuals randomised to semaglutide than to placebo (50 vs 29 participants; 3.0% vs 1.8%; $P=0.02$).¹

Comparison with other semaglutide trials

- No difference in rates of retinopathy adverse events was observed between semaglutide and its comparators in the SUSTAIN 1–5 trials, or in Japanese regulatory trials.²
- The majority of adverse retinopathy outcomes in SUSTAIN 6 were attributed to a large and rapid fall in HbA_{1c} during the first 16 weeks of the trial.
- These events were seen in individuals with pre-existing retinopathy who had a high HbA_{1c} at baseline and were already receiving insulin.
- In the other semaglutide trials, participants with existing diabetic retinopathy requiring active medical treatment were excluded, and these trials also had upper HbA_{1c} limits of 86–91 mmol/mol (10.0–10.5%) for inclusion. Neither of these exclusion criteria applied to SUSTAIN 6.
- In a meta-analysis of six placebo-controlled and seven active-control studies of semaglutide, the odds ratio for retinopathy outcomes was 1.32 (95% CI, 0.98–1.77). However, this was largely driven by the outcomes in SUSTAIN 6.³

Retinopathy and other GLP-1 RAs

The view that the retinopathy results from a large, sudden fall in HbA_{1c} is supported by data on two other powerful glucose-lowering drugs in the class, liraglutide and dulaglutide:

- In LEADER, there was a non-significant 15% increase in retinopathy events in participants who were randomised to liraglutide.⁵
- In REWIND, there was a non-significant 24% increase with dulaglutide.⁶ This trial had an upper HbA_{1c} limit of 81 mmol/mol (9.6%) for inclusion.

Take-home recommendations

The author has adopted the following recommendations in Swansea Bay University Health Board for initiation of semaglutide (both injectable and oral), and all other GLP-1 RAs.

Caution is urged in patients with:

- Diabetic retinopathy requiring active ophthalmology follow-up (see [Diabetic retinopathy factsheet](#) for more information on classification and management).
- Poor glycaemic control: HbA_{1c} >91 mmol/mol (10.5%).
- Current insulin treatment.

The word “caution” means that the ophthalmology review should be up to date, with arrangements for appropriate follow-up, and that the ophthalmology team should be informed of the proposed therapy change.

In people without significant retinopathy (e.g. those on an annual review for eye screening), being on insulin or having poor control alone do not imply risk. Ideally, retinopathy screening should occur every 12 months, or up to 18 months allowing for slippage in local screening appointments. If the previous retinal screen was completely normal, at present an interval of up to 24 months is acceptable. Longer than this and active retinopathy may be present, so the retinal screen should be updated before GLP-1 RA initiation.

Actively encourage retinal screening attendance at every review.

Some case scenarios demonstrating how to put these recommendations into practice can be found in **Box 1** overleaf.

- No significant difference in risk of retinopathy outcomes was observed in the cardiovascular outcomes trial of oral semaglutide.⁴ **Individuals with pre-existing retinopathy were excluded from the trial.**
- Guidance regarding the early worsening of retinopathy is contained in the Prescribing Information for insulins. Similar recommendations for other potent glucose-lowering medications, such as semaglutide, may be appropriate.

Post-approval studies

To date, one post-approval pharmacovigilance study has been published. Fadini and colleagues evaluated the link between GLP-1 RAs and adverse events in the FDA Adverse Event Reporting System (FAERS) from 2004 through to Q1 2017:⁷

- A total of 114 814 reports which included GLP-1 RAs as suspect or concomitant drugs were compared with 694 725 reports involving other glucose-lowering therapies.
- The cumulative frequency of retinal adverse events was 2.53 per 1000 reports for GLP-1 RAs, compared with 6.62 per 1000 reports for other medications, (reporting ratio, 0.38; 95% CI, 0.34–0.43; $P < 0.01$).
- This finding was consistent irrespective of concomitant glucose-lowering therapy (including insulin) and was seen for each of the GLP-1 RAs.
- Interestingly, the reports involving GLP-1 RAs listed significantly more comorbid conditions and concomitant medications, but despite this, the frequency of retinal adverse events was still significantly lower.

Although analyses of the FAERS database are often criticised due to biases in reporting, the publicity following the SUSTAIN 6 data might have been expected to increase the number of retinopathy reports with GLP-1 RAs, especially those in association with semaglutide.

Focus study

The European Medicines Agency has requested a randomised controlled trial specifically to investigate the impact of semaglutide on diabetic retinopathy ([ClinicalTrials.gov Identifier NCT03811561](https://clinicaltrials.gov/ct2/show/study/NCT03811561)). The primary endpoint is retinopathy progression and there will be 17 secondary retinal endpoints. The study is estimated to complete in 2025.

Conclusions

The most concerning safety issue of semaglutide use is that of worsening diabetic retinopathy. This was not seen in the Phase 3a clinical trial programme (SUSTAIN 1–5 and 7) but emerged as an unexpected finding in the cardiovascular outcomes trial for semaglutide, SUSTAIN 6.

The author strongly believes that the retinopathy signal for semaglutide was the result of a rapid reduction of hyperglycaemia in trial subjects with pre-existing (typically advanced) retinopathy and very poor glycaemic control, on a background of insulin therapy. This view is consistent with previous reports of early worsening of diabetic retinopathy with insulin treatment in

the DCCT (Diabetes Control and Complications Trial) and in pregnant women, as well as in people who have undergone bariatric surgery.⁸ There is also a reassuring paucity of GLP-1 receptors in the retina,⁹ making a direct drug effect less likely.

The problem for clinicians prescribing for people with type 2 diabetes and pre-existing retinopathy is that the impact of GLP-1 RAs on glucose lowering is highly variable, with some individuals having a dramatic response even at low starting doses. This is in contrast to insulin, where slow up-titration from a low starting dose can effect a gradual improvement in glucose control in almost all cases.

Box 1. Case scenarios and recommendations.

Patient A: HbA_{1c} 98 mmol/mol (11.1%), no insulin, has retinopathy under the care of an ophthalmologist. **Discuss with ophthalmologist prior to initiating the GLP-1 RA.**

Patient B: HbA_{1c} 110 mmol/mol (12.2%), no insulin, did not attend last retinal screening 14 months ago and had background retinopathy on screening 26 months ago. **Request urgent retinal screening prior to initiating GLP-1 RA.**

Patient C: HbA_{1c} 93 mmol/mol (10.7%), taking insulin (Abasaglar), normal retinal screening 12 months ago. **Initiate GLP-1 RA, expedite retinal screening and encourage attendance.** (Note: Uncommon scenario in primary care since ADA/EASD Consensus encourages initiation of GLP-1 RA as first injectable unless there are osmotic symptoms/weight loss).

Patient D: HbA_{1c} 98 mmol/mol (11.1%), no insulin, normal retinal screening 16 months ago. **Initiate GLP-1 RA, request routine retinal screening and encourage attendance.**

Patient E: HbA_{1c} 104 mmol/mol (11.7%), no insulin, recently joined your list, says had retinal screening “recently” and his “eyes are fine”, you are planning to start oral GLP-1 RA. **Get previous retinal screening results then decide whether urgent retinal screening is required prior to initiation GLP-1 RA.**

Patient F: HbA_{1c} 93 mmol/mol (10.7%), no insulin, referred from retinal screening to ophthalmology with pre-proliferative retinopathy 15 months ago but no eye clinic letter in electronic record. **Check whether seen in ophthalmology clinic and, if so, discuss suitability for GLP-1 RA; if not, chase urgent ophthalmology appointment and discuss suitability for GLP-1 RA prior to initiation. Ensure patient understands importance of attending eye clinic appointment.**

Patient G: HbA_{1c} 86 mmol/mol (10.0%), has been referred from retinal screening but not yet seen by ophthalmology. **Wait for the result of the consultation or let ophthalmology know of the plan to initiate.**

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