Tirzepatide treatment associated with increased proliferative retinopathy but possible reduced new retinopathy

This real-world, retrospective cohort study, published in *Diabetologia*, compared 3455 people initiating tirzepatide with 3454 matched controls to determine the effects of the GIP/GLP-1 receptor agonist on risk of retinopathy. New-onset proliferative diabetic retinopathy (PDR), with or without maculopathy, was more common with tirzepatide (1.1% vs 0.5%; adjusted odds ratio 2.15), and mostly occurred in those with moderate-to-severe or mild non-proliferative retinopathy with maculopathy (R2M1 or R1M1) at baseline. In people without retinopathy at baseline, however, tirzepatide was associated with a significantly reduced risk of developing new retinopathy (odds ratio 0.73), and there was no significant association with retinopathy progression in those treated with tirzepatide who had mild, non-proliferative diabetic retinopathy (R1MO or R1M1) at baseline. The authors recommend that in people with maculopathy and/or moderate-to-severe diabetic retinopathy, discussion with their ophthalmologist should be considered prior to initiating tirzepatide. The findings remind us that we should review retinal screening reports prior to prescribing, and to warn people to seek urgent medical advice if they suffer any eye symptoms during treatment with semaglutide or tirzepatide.

Pam Brown
GP in Swansea

It has been known since 1998 that intensive glucose lowering reduces the risk of diabetic retinopathy (UK Prospective Diabetes Study Group, 1998). However, rapid reductions in glycaemia, which may occur with insulin therapy, injectable incretin drugs for type 2 diabetes or after bariatric surgery, may cause early worsening of diabetic retinopathy (EWDR). In the SUSTAIN-6 trial of semaglutide for type 2 diabetes, EWDR occurred with significant glucose reductions, particularly in participants who were also receiving insulin or who had more than background retinopathy at baseline (Marso et al, 2016).

In a previous meta-analysis, risk factors for EWDR included higher baseline HbA_{1c}, greater HbA_{1c} reduction, longer duration of diabetes and greater than background retinopathy at baseline (Feldman-Billard et al, 2018). The authors recommended eye monitoring every 3 months for those at high risk of EWDR during intensive glucose-lowering, although this is not yet included in guidelines.

In the case of tirzepatide, a recent meta-analysis of the SURPASS clinical trial programme did not identify any increased risk of EWDR (Popovic et al, 2024); however, no additional retinal surveillance was undertaken during the studies and people with proliferative retinopathy, severe pre-proliferative retinopathy or maculopathy were excluded.

Since tirzepatide is known to have potent glucose-lowering effects, the present study, published in *Diabetologia*, sought to clarify the impact of the drug on EWDR across all retinopathy groups.

Study design

In this real-world, retrospective cohort study, Buckley and colleagues compared 3455 people who had received tirzepatide for at least 180 days with 3454 people who had not been exposed to tirzepatide, matched for sex, retinopathy status, retinal screening history, diabetes duration, HbA_{1c} and glucose-lowering treatment. All study participants already had tight glycaemic control, with a mean HbA_{1c} of 56.1 mmol/mol (7.3%) across the groups at baseline.

Results

Retinal outcomes are summarised in *Table 1*. **New-onset proliferative diabetic retinopathy**

Citation: Brown P (2025) Diabetes Distilled: Tirzepatide treatment associated with increased proliferative retinopathy but possible reduced new retinopathy. *Diabetes & Primary Care* **27**: [Early view publication]

Practice points

1. In people with existing moderate-to-severe retinopathy, treatment with tirzepatide is associated with a significantly increased risk of worsening diabetic retinopathy.
2. Before initiating a GLP-1 or GIP/GLP-1 receptor agonist, ensure retinal screening is up to date and review results.
3. For anyone who has more than background diabetic retinopathy, discuss suitabililty with ophthalmology prior to initiation.
4. It is important to code retinopathy results accurately, and to warn those who may be at increased risk of new proliferative diabetic retinopathy not to buy incretin-based therapies privately for weight loss.
5. Further information on diabetic retinopathy and semaglutide will be available from the FOCUS and ANGIOSAFE2 studies.

Table 1. Summary of retinal outcomes.

Complication	Baseline	Tirzepatide recipients	Unexposed to tirzepatide	Adjusted odds ratio [95% CI]	Conclusion
New-onset proliferative diabetic retinopathy*	R0M0, R1M0, R1M1, R2M0 or R2M1 (No proliferative retinopathy)	33 (1.1%)	17 (0.5%)	2.15 [1.24–3.74]	Significant increased risk of proliferative retinopathy (R3M0 or R3M1)*
New-onset retinopathy	R0M0 (No retinopathy)	128 (6.9%)	181 (9.3%)	0.73 [0.62–0.86]	Apparent protective effect on development of new retinopathy
New-onset maculopathy	R0M0, R1M0 or R2M0 (No maculopathy)	84 (3.4%)	85 (3.4%)	1.02 [0.82–1.26]	No significant association with increased maculopathy
Retinopathy progression	R0M0 or R0M1 (No retinopathy) or R1M0 or R1M1 (Mild non-proliferative retinopathy)	49 (4.7%)	37 (3.4%)	1.29 [0.89–1.88]	No significant association with retinopathy progression

*Combined PDR incidence was 6.9 per 1000 person-years.

(**PDR**), with or without maculopathy, was **more common with tirzepatide**, occurring in 33 tirzepatide recipients and in 17 of those without exposure (1.1% vs 0.5%). After adjustment for established risk factors, this gave an odds ratio (OR) of 2.15. Most of the new PDR occurred in those with moderate-to-severe (R2M1) or mild (R1M1) non-proliferative retinopathy with maculopathy.

In people **without retinopathy** at baseline, tirzepatide treatment was associated with significantly **reduced** odds of developing new retinopathy (OR 0.73).

There was **no significant association** between tirzepatide and retinopathy progression in those who had **mild, non-proliferative diabetic retinopathy** (R1MO or R1M1) at baseline.

In those **without maculopathy** at baseline, tirzepatide treatment demonstrated **no increased association with developing maculopathy**.

Discussion

The mean interval to diagnosis of PDR was 325±143 days in those treated with tirzepatide, meaning that worsening can occur later in treatment, even on stable doses.

The SURPASS clinical trial programme identified a low rate of PDR: only 21 adverse retinal events in those treated with tirzepatide compared with 19 in controls, thus implying no increased risk with tirzepatide. In this real-world study, however, there was an increased incidence of PDR in those exposed to tirzepatide. New PDR occurred in 17 out of 113 people (15%) treated with tirzepatide who had R2M0 or R2M1 at baseline, and there was a higher risk of PDR in those with maculopathy at baseline. Both of these are groups who should already be receiving specialist ophthalmology follow-up in the UK.

In a *post hoc* analysis of the SUSTAIN-6 trial of semaglutide, the degree of glycaemic reduction at 16 weeks correlated with the risk of new retinopathy (Vilsbøll et al, 2018), whereas in this real-world study, HbA_{1c} reduction was not independently associated with increased odds of PDR, possibly due to the already low HbA_{1c} at baseline.

Study strengths and limitations

Limitations include those of all real-world cohort studies, including possible additional confounders. The tirzepatide cohort had mostly transitioned from a GLP-1 receptor agonist to tirzepatide and, therefore, already had a mean HbA_{1c} of 55.2 mmol/mol (lower than would be usual for new initiations of an injectable incretin drug, including in the SURPASS clinical trials), and this also resulted in low initial HbA_{1c} reductions. Thus, these results may underestimate changes associated with tirzepatide in current clinical practice.

Strengths include the large size of the cohort and good matching with controls. There was consistent annual retinopathy examination, rather

than just the retinal adverse event reporting that occurred in many of the clinical trials, and this allowed optimised diagnosis of EWDR.

The authors recommend that in people with maculopathy and/or moderate-to-severe diabetic retinopathy, discussion with their ophthalmologist should be considered prior to initiating tirzepatide. However, in people with background retinopathy only, tirzepatide was not associated with significant worsening of retinopathy in this study, so they do not believe any specific action is required.

For those with no retinopathy, tirzepatide treatment appeared to be associated with a reduction in risk of new retinopathy, and further studies will be needed to confirm this potential added benefit of tirzepatide, presumably linked to effective glycaemic control.

Implications for practice

This paper provides important guidance to inform safe initiation of tirzepatide in people with type 2 diabetes who already have more than background retinopathy. Although tirzepatide appears to protect against the development of new diabetic retinopathy and was not associated with increased risk of maculopathy compared to those not receiving tirzepatide, in people with existing moderate-to-severe retinopathy, treatment was associated with a significantly increased risk of new PDR. In this study, the risk appeared to be independent of rapid HbA_{1c} reduction, a mechanism previously confirmed to increase PDR risk, suggesting that caution is required irrespective of HbA_{1c} when initiation is being considered.

Advice issued following analysis of SUSTAIN-6 recommended that, if HbA_{1c} was >91 mmol/mol (10.5%) in those with more than background retinopathy, glycaemia should be reduced slowly with other glucose-lowering agents before starting semaglutide (either injectable or oral, since these have comparable efficacy) (Bain, 2021). Since its launch, tirzepatide guidance has been similar, although without firm supporting evidence.

These new findings, particularly since they occurred even in people with well-controlled HbA_{1c} at baseline, are a reminder that, in those known to have more than background diabetic retinopathy, we should discuss use of tirzepatide with their ophthalmologist prior to initiation.

Worryingly, third parties are prescribing tirzepatide for weight loss in people with diabetes, some of whom may have significant retinopathy and/or maculopathy, without access to the person's full medical record. It is important to code retinopathy results accurately, and to warn those who may be at risk not to buy tirzepatide privately for weight loss without discussion with their eye specialist.

With the UK retinopathy screening interval increased to 2 years for those with no retinopathy on two annual screens, concerns have been raised about the risk of delay in diagnosis of sight-threatening retinopathy in younger adults, and in Black and South Asian groups labelled as low-risk (Olvera-Barrios et al, 2023). It will be important to understand more about the risks of developing maculopathy and moderate-to-severe retinopathy in the interval between screenings, particularly in people with a persistently high HbA_{1c}, and how this should influence our assessment of PDR risk in those without a recent retinal screen who initiate tirzepatide.

Further data on the risks of diabetic retinopathy associated with incretin therapies will be published from the FOCUS study (semaglutide) and the ANGIOSAFE2 study (semaglutide and tirzepatide).

Considering the possible risks of EWDR, it is crucial that we review retinal screening reports prior to prescribing. Furthermore, in view of the ongoing uncertainty around whether incretin drugs increase the risk of non-arteritis anterior ischaemic optic neuropathy (NAION) (Etminanet al, 2025), we need to warn people to seek urgent medical advice if they suffer eye symptoms during treatment with these drugs. Such a warning may improve understanding of the importance of retinal screening.

We need to help people protect their vision whilst also supporting appropriate access to tirzepatide and its potential benefits. This paper helps us to achieve that. ■

Early worsening of diabetic retinopathy in individuals with type 2 diabetes treated with tirzepatide: A real-world cohort study

Read the article in full
(open access)

References

Bain SC (2021) At a glance factsheet: GLP-1 receptor agonists and diabetic retinopathy. *Diabetes & Primary Care* **23**: 103–4

Buckley AJ, Tan GD, Gruszka-Goh M et al (2025) Early worsening of diabetic retinopathy in individuals with type 2 diabetes treated with tirzepatide: A real-world cohort study. *Diabetologia* 10 Jul [Epub ahead of print]. https://doi.org/10.1007/s00125-025-06466-8

Etminan M, Sodhi M, Maberley D (2025) GLP-1 RAs and nonarteritic anterior ischemic optic neuropathy – Making sense of the data. *JAMA Ophthalmol* **143**: 220–1

Feldman-Billard S, Larger É, Massin P; SFD Study Group (2018) Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. *Diabetes Metab* **44**: 4–14

Marso SP, Bain SC, Consoli A et al; SUSTAIN-6 investigators (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* **375**: 1834–44

Olvera-Barrios A, Rudnicka AR, Anderson J et al; ARIAS Research Group (2023) Two-year recall for people with no diabetic retinopathy: A multi-ethnic population-based retrospective cohort study using real-world data to quantify the effect. *Br J Ophthalmol* **107**: 1839–45

Popovic DS, Patoulias D, Karakasis P et al (2024) Effect of tirzepatide on the risk of diabetic retinopathy in type 2 diabetes. *Diabetes Obes Metab* **26**: 2497–500

UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53

Vilsbøll T, Bain SC, Leiter LA et al (2018) Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab* **20**: 889–97