Title: Addressing the risk of ocular complications of GLP-1RAs; a multi-disciplinary expert consensus

Short running title: Ocular complications of GLP-1RAs: expert consensus

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Abstract

Aims: There is current apprehension amongst some clinicians, and conflicting evidence regarding ocular complications in relation to Glucagon-like peptide-1 receptor agonists (GLP-1RAs). We aimed to generate multi-disciplinary, expert-led consensus recommendations, relating to ocular complications, to facilitate optimum prescribing of GLP-1RAs.

Materials and Methods: A modified Delphi was conducted following the ACcurate COnsensus Reporting Document (ACCORD) for Delphi research. A structured literature review informed an anonymous online Delphi questionnaire, followed by a virtual consensus meeting. Eligible participants included ophthalmologists, diabetologists, and obesity specialists practising in Europe.

Results: Responses from 58 participants across 17 countries were analysed. Respondents agreed that diabetic retinopathy (DR) worsening events are primarily linked to rapid blood glucose-lowering, rather than a direct drug effect. The benefits of GLP-1RAs were deemed to outweigh potential ocular risks and should not limit access to these medicines. Prescribers should ensure that people with diabetes are screened for diabetic retinopathy before commencing GLP-1RAs particularly in high risk populations (>10 years duration and/or poor glucose control, (haemoglobin A1c [HbA1c] >10% or 86mmol/mol)). When prescribing GLP-1RA to those with sight loss in one eye and/or prior history of non-arteritic anterior ischemic optic neuropathy (NAION), risk of ocular complications should be discussed. The Delphi study highlighted current uncertainty in the evidence, with some topics on the relationship between GLP-1RAs and ocular complications reaching limited consensus.

Conclusions: Further research is needed into the direct effects of GLP-1RAs on the retina and ocular complications. New evidence should be disseminated rapidly to optimise outcomes and safety.

Key words: Glucagon-like peptide-1 receptor agonists, non-arteritic anterior ischemic optic neuropathy, diabetic retinopathy, consensus recommendations, Delphi

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established, effective therapeutic class of glucose-lowering drugs which have been used in the treatment of type 2 diabetes mellitus (T2DM) since 2005.[1] Following evidence demonstrating overwhelming benefits on body weight, the GLP-1RAs semaglutide and liraglutide were approved as weight loss agents for adults with obesity.[2] Additionally, treatment with GLP-1RAs show significant reductions in risk of major adverse cardiovascular events and its individual components.[3,4] Despite these benefits the risk of adverse events should be considered. In particular, there is current debate and apprehension among some clinicians regarding ocular complications.[5] Significantly higher rates of retinopathy events were observed in those assigned semaglutide as compared with placebo in a large, randomised controlled trial (RCT) (SUSTAIN 6).[6] Additionally, recent retrospective real-world studies have reported an association between semaglutide and non-arteritic anterior ischemic optic neuropathy (NAION), but this is not confirmed in other studies.[7-9]

Finally, it should be noted that data from a cohort of over 77,000 participants demonstrated no overall association between the use of GLP-1RAs and incident diabetic retinopathy (DR), and a decreased risk when compared with insulin.[10] Furthermore, a post-approval pharmacovigilance report found the frequency of retinal adverse events to be significantly lower with GLP-1RAs as compared with other glucose lowering medications.[11] Nonetheless, the European Medicines Agency have requested a trial to investigate the impact of semaglutide on diabetic retinopathy, which is ongoing; however, study completion is not anticipated until November 2027.[12] Furthermore, UK NHS guidance on ocular complications related to

GLP1-RA use is under development but not yet published, hence there is a need for expert consensus to understand the clinical implications of GLP-1RA use and ocular complications in order to support optimal clinical decision making.

We aimed to formulate expert-led consensus recommendations on the risk versus benefits of GLP-1RAs, focusing on ocular complications, to facilitate optimum management of GLP-1RAs and support clinical decision-making.

Materials and Methods

A modified Delphi approach, a systematic, reliable, and widely accepted methodology for healthcare decision making in the absence of robust clinical evidence, was adopted to create formal consensus recommendations. Figure 1 provides an overview of the study flow. The study included one anonymous online questionnaire and one consensus meeting; with key aspects of a Delphi being followed, including iteration, and statistical stability of consensus. To ensure robustness and credibility, we followed the ACcurate COnsensus Reporting Document (ACCORD) for Delphi research.[13] Prior to study initiation, a Delphi panel (herein referred to as panellists) was convened, including an expert steering committee (ME, RS, MLA, IP) who facilitated development of the Delphi study, alongside further experts (SCB, DS, CD, SJD, PB) who also completed the Delphi questionnaire.

Delphi participants

Ophthalmologists, diabetologists, and obesity specialists practising in Europe were eligible to participate. Potential participants were identified from published literature via a targeted search. Members of the European Association for Diabetic Eye Complications (EAsDEC) mailing list and of the Association of British Clinical Diabetologists (ABCD), (via the April 2025 newsletter), were also invited to participate in the online Delphi questionnaire.

We completed the Health Research Authority (HRA) and UK Medical Research Council (MRC) decision tool to determine the research did not require ethics committee approval (supplementary material). Participation was voluntary and no renumeration was offered. Participants were provided with instructions for completion, provided informed consent and were made aware that their responses were anonymous.

Evidence generation

A rapid targeted literature review was performed using a formal, structured search strategy, developed for the electronic database Medline via the Ovid platform (supplementary material). Search terms included Glucagon-like peptide-1 receptor agonists, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide and tirzepatide; however we did not include albiglutide. Albiglutide has been discontinued and was not considered relevant for this review, nor was it discussed during development of the recommendations.[14] Searches were restricted to English language publications, to those published from 01 January 2014 to 15 November 2024, and with Ovid's Clinically Useful Journals Filter.[15] In addition, a non-systematic search was performed using free-text terms, including diabetes, obesity, glucose regulation, weight loss, adverse events, ocular disease, GLP-1RAs, retinopathy, and ophthalmology.

Online questionnaire

Delphi statements were drafted based on the evidence generation activities and revision by the expert steering committee. The Delphi questionnaire comprised 39 questions/statements which established eligibility and consent, participant information, potential benefits of GLP-1RAs, frequent adverse events (including non-ocular conditions), discontinuation, populations at risk of ocular events, and prescribing to at-risk populations (see supplementary material). Participants were asked to rate each statement based on their own opinion and clinical experience. The statements were structured as a 7-point Likert scale. Additional questions included participants assigning a score between one and ten to indicate the likelihood of risk

of events or prescribing to specific populations. Participants were able to state they did not have sufficient knowledge to provide a rating and were encouraged to provide further explanation in free-text spaces. Responses were consolidated and analysed to establish the level of consensus amongst participants. A pre-determined level of ≥75% agreement was considered to have good consensus, 60–74% agreement to show some consensus, and <60% agreement showed no consensus. Whilst no standard percentage to assess consensus exists, 75% has been reported as the median threshold used.[16]

Consensus meeting

Consolidated outcomes from the Delphi questionnaire were presented for discussion by the panel at an online conference meeting; results were presented and the panellists considered comments provided by the Delphi participants to aid understanding and derive final recommendations.

Results

Delphi participants

The online Delphi questionnaire was open from 03 March 2025 to 14 April 2025, during that time 89 individuals interacted and logged onto the questionnaire. Of these, four individuals were excluded during the eligibility assessment, 27 completed the eligibility/participant information only, and were excluded from the analysis. In total 58 responders either fully (n=45) or partially (n=13) completed the questionnaire and were included in the analysis.

Participants were relatively equally split across disciplines; 25 ophthalmologists, 19 diabetologists, 11 were specialists in diabetes and obesity, one was an obesity specialist, and two stated ‘other’. Most participants were from England (n=17) and Wales (n=9). Other locations included Italy (n=8), Spain (n=6), France (n=3), Denmark (n=2), Germany (n=2), N.

Ireland (n=2), Albania (n=1), Croatia (n=1), Georgia (n=1), Greece (n=1), Montenegro (n=1), Russia (n=1), Scotland (n=1), Sweden (n=1), and Switzerland (n=1).

The concepts agreed and consensus recommendations made by the Delphi panel are presented alongside a narrative summary capturing the Delphi participants and panellists' discussion below.

Treatment effect of GLP-1RAs

In line with the substantial published evidence, there was good consensus that GLP-1RAs are effective for glucose management (94%), weight loss (94%) and reducing the risk of major cardiovascular events (96%). There was also good consensus (80%) that GLP-1RAs can prevent development of T2DM in those who are considered pre-diabetic (Table 1). The Delphi participants referred to *"numerous RCTs and meta-analysis"* published supporting the treatment effects of GLP-1RAs. Indeed, a recent network meta-analysis showed that all GLP-1RAs significantly reduced HbA1c from baseline as compared to placebo. Reporting more significant reductions in both HbA1c and fasting blood glucose with long-acting GLP-1RAs as compared to short-acting GLP-1RAs; with tirzepatide, semaglutide and liraglutide demonstrating the greatest improvements in glucose control .[17] It should also be clarified that not all GLP-1RAs are equally effective for weight-loss, with tirzepatide, semaglutide and liraglutide generally demonstrating the greatest reductions in body weight.[17-19] Additionally, the effect of GLP-1RAs on reducing CV events differs between agents; liraglutide, dulaglutide and semaglutide have all shown significant reductions in CV events, and data on tirzepatide is due to be published in the near future.[3,20,21]

The participants also agreed (80%) that 'the effectiveness of blood glucose-lowering in patients with T2DM is influenced by the method of GLP-1RA administration and their comments reflected the current literature,[22] *"oral method still lowers blood glucose but doesn't lower as*

quickly in most people". However, there are no large head-to-head studies, thus robust direct comparisons cannot be made.[23] Importantly there was also good consensus on the use of robust real-world evidence to influence clinical practice, both in relation to efficacy (92%) and safety (94%) outcomes. Reflecting awareness of ongoing evidence generation, participants noted *"I have not seen much in the way of robust, well designed real-world evidence reporting safety outcomes. There are some real-world studies that have been published raising concerns, such as data on NAION, but the data in this space is not the most robust".*

Overall adverse events and discontinuation

Delphi participants listed 'nausea, vomiting, abdominal pain, gastroesophageal reflux, and gastritis as the most frequent adverse events and the most common cause of discontinuation in relation to GLP-1RA therapy. Several participants also added '*diarrhoea and constipation'*. Participants were asked to state if they believed that GLP-1RAs had a positive, negative or no effect on several other conditions; only gastrointestinal events reached good consensus (Table 2). Although the same events were listed for frequency and discontinuation, the panellists discussed that though frequent, some events can be acute and do not always lead to discontinuation. Additionally, the statement 'people with T2DM are more likely to discontinue GLP-1RA therapy as compared with other diabetes treatments' did not reach consensus (42%). Participants comments also reflected the balance between treatment effect and discontinuation, in that *"if patients lose weight, they are inclined to continue therapy".* The panellists agreed with this, and expressed it is generally a balance between observed benefits and tolerance of adverse events such as nausea.

Ocular events

There was limited consensus between participants on the effect of GLP1-RA therapy across ocular conditions (Table 3), suggesting current uncertainty in this area. Based on the results

and discussion, the panellists developed several recommendations to support GLP-1RA management and future research (Table 4*Table 4. Multi-disciplinary consensus recommendations on GLP-1RAs and ocular events*).

Diabetic retinopathy

There was some consensus (68%) that GLP-1RAs have a negative effect on the worsening of DR and progression to vision-threatening disease, in particular in those patients with advanced stages of DR. Many comments regarding the early worsening of DR showed that participants believe the effect is due to *"base-line eye status"* and *"likely related to the drop in A1c"*. The Delphi panellists further corroborated this viewpoint; progression and development of DR is generally associated with poor glycaemic control and duration of diabetes,[24] with retinopathy worsening events associated with rapid reductions in HbA1c.[25,26] Multiple systematic reviews and network meta-analysis have shown significant reductions in HbA1c with GLP-1RA treatment; yet, despite differences in magnitude of reduction in HbA1c between GLP-1RAs, [17,27] [17,27] a recent real-world observational study found no difference in risk of DR following initiation of liraglutide, dulaglutide, or exenatide in people with T2DM.[28] However, several studies have demonstrated an increased risk of DR with semaglutide and tirzepatide specifically,[6,29] which may reflect their efficacy within the GLP-1RA class, underpinning the observed early worsening effect. Understanding the potential differences between GLP-1RAs in respect to ocular complications is an important consideration for future research. Though the majority of GLP-1RA prescribing is currently focused on long-acting GLP1-RAs, there are multiple agents in late stage development, adding further imperative to our approach to evaluate risk versus benefit in clinical practice.

The ophthalmologists on the panel noted that early worsening is a concept they are aware of as a professional; therefore, are likely to accept this may occur with new therapies. Noting that

data on early worsening has long been reported in relation to insulin, and that rapid lowering of blood glucose can lead to deterioration of retinopathy, but this may be transient.[25,30,31] The phenomenon of transient early worsening was first demonstrated in the Oslo study, where people without proliferative retinopathy were randomised to different insulin regimens. Initial deleterious effects to the retina were observed in those who experienced a rapid and large fall in blood glucose; however, improvements in retinopathy outcomes were subsequently observed,[30] with seven-year follow-up data demonstrating that long-term improved blood glucose control slowed progression of retinopathy.[32] A similar effect of increased rates of DR was observed with semaglutide in the SUSTAIN 6 study[6] this effect was considered likely attributable to the magnitude and rapidity of HbA1c reduction over the first 16 weeks.[31] In addition, data showed that incidence rates of confirmed DR were greater for people with HbA1c reductions >1.5% treated with semaglutide or placebo.[31] Interestingly, the majority of people with confirmed DR events were also treated with insulin, which may be an indication that these individuals had longer duration of diabetes and high baseline HbA1c, which are suggested risk factors for developing DR.[24,31]

The discussion was strengthened by strong consensus (94%) observed on the statement 'retinopathy worsening events in relation to GLP-1RA therapy are mainly caused by the rapid blood glucose-lowering effect of treatment'. Several, some comments from participants supported this view, *"I believe the evidence shows there may be temporary early worsening….but in the long term better glycaemic control results in better diabetic retinopathy outcomes"*. However, there was no consensus (58%) that the risk of DR worsening is limited to the first 12 months of treatment with GLP-1RAs. Overall, most comments supported the hypothesis, *"I believe this to be true, but I don't have data"*, *"In those with high HbA1c and established retinopathy, it may deteriorate at the beginning, but again likely there will be benefit in the long-term"*. The panellists agreed that the definition of early worsening varied

across publications, but it is typically shorter than 12 months, with most evidence suggesting three to six months.[30,31] The panellists raised concerns regarding insufficient awareness around the timeframe for 'early worsening' and identified a potential need for improved education in this area.

Despite good consensus that retinopathy worsening events are mainly caused by rapid blood glucose-lowering effect, there was less agreement regarding other potential mechanisms of action. The statement 'GLP-1RA therapy could cause damage to the retina, but it is not attributable to the drugs themselves' achieved some agreement (68%). The comments largely agreed, and reflected current lack of evidence, *"no data to support this yet"* and *"it is unlikely a direct cause"*. Evidence suggests that GLP-1 receptor expression exist in normal eyes,[33] but is less detectable in proliferative DR:[34] therefore, the direct effect of GLP-1RAs on advanced DR is unclear. Furthermore, there was also some agreement (65%) on the statement 'GLP-1RA treatments mitigate inflammatory response in the retina and protect retinal cells from degeneration'. Comments from the participants mirrored the level of consensus observed on the statement, *"anti-inflammatory effects have been demonstrated in other end organs"* as compared with *"this is speculation"*. The panellists discussed discrepancies in opinions and supported the overall uncertainty, stating, that there is good experimental evidence for these mechanisms in animal models;[34] however, clinical trials are lacking. Again, the panel recommend further research is needed, specifically concerning inflammatory markers like hyperreflective foci.[35]

NAION

There was no consensus that GLP-1RA therapies have a negative effect, in terms of increasing the risk, of NAION (41% agreed a negative effect whilst 52% stated there was no effect). The result and comments from the participants reflect the current uncertainty in the literature on this topic, with participants noting there is currently no evidence *"of a causative link"* and that

"NAION has some data suggesting a negative effect, but this still leaves room for doubt". The panellists agreed with these comments, noting that the results show a growing awareness of a potential association. Noting that increased NAION risk has been associated with both tirzepatide and semaglutide;[7,29] however, no causal link has thus far been established. Although no definitive evidence on causality currently exits, there is physiological plausibility, thus they agreed a recommendation for further research, and any new evidence on GLP-1RAs and NAION should be clearly and rapidly reported.

Other ocular events

There was strong agreement among Delphi participants that there is no effect on keratitis (94%) or glaucoma (87%); however, there was no agreement regarding new-onset DR (43% positive effect, 41% no effect and 16% negative effect), non-proliferative DR (41% no effect, 35% positive effect, and 24% negative effect) or macular oedema (48% no effect, 38% negative effect and 14% a positive effect). The panellists agreed this lack of consensus likely reflects that there are insufficient data on these specific events. Nevertheless, the neuroprotective effects of GLP-1R agonists have been demonstrated in experimental models of glaucoma, and further research is warranted.[36]

Populations at increased risk of ocular events

There was strong agreement (94%) for the statement that 'people with advanced stages of DR are at a greater risk of disease worsening/progression on GLP-1RA therapy'. The panellists agreed with this opinion and discussed that people with advanced stages of DR (i.e., proliferative and sight-threatening DR) have been excluded from trials after the SUSTAIN 6 results,[6] thus, determining causal effects is difficult. Recent evidence has demonstrated tirzepatide being associated with new onset proliferative DR in those with T2DM; however, reduced odds of new onset retinopathy in those without DR was observed.[29] It should also be

considered that there is evidence that the rapid reduction of HbA1c may not be associated with progression of mild or moderate non-proliferative DR.[26]

Delphi participants were further asked to state the likelihood of different patient groups being considered to have an increased risk of ocular events if receiving GLP-1RAs and asked in which population groups they would not consider prescribing GLP-1RAs. Overall, the results varied; however, the population considered at highest risk were patients already diagnosed with proliferative DR, followed by those with prolonged duration of T2DM (≥10 years), and those with elevated HbA1c (≥6·5% or ≥48mmol/mol). It should be noted that one participant highlighted *"≥6·5% is not very high"*. The panel agreed and their recommendation takes this into consideration, referencing HbA1c >10% or >86mmol/mol.

Importantly Delphi questionnaire results and the panellist discussion reflect that those individuals most at risk of ocular complications are most likely to benefit from GLP-1RA therapy. The overwhelming benefits to these individuals must be considered, the benefits of GLP-1RAs were deemed to outweigh potential ocular risks and should not limit access to treatment. The panellists highlighted that not all people on GLP-1RA therapy are at an increased risk of ocular events; for example, people without diabetes and people with low HbA1c (<6·5% or <48mmol/l). When considering the overall number of people on GLP-1RAs, there is likely little effect of the worsening or progression to DR. The panellists supported comments from participants which noted DR and macular oedema are both treatable conditions, with timely intervention; therefore, these should not be a barrier to prescribing GLP-1RA therapy.

The panellists raised concerns that the rapid increase in access to GLP-1RA agents through over the counter purchasing and online services for weight management, may present a risk of early worsening retinopathy in people with undiagnosed T2DM, potentially coupled with

unidentified retinopathy. As such the panel recommend stricter regulations and monitoring around over the counter GLP-1RA use.

Interestingly, people with a history of NAION were not rated as high risk of ocular events. The ophthalmologists on the panel discussed the severe consequence of NAION, as it is non-reversible, thus it is important to identify people with prior NAION or at high risk for NAION before GLP-1RA initiation. It was noted that several risk factors such as a crowded optic disc (i.e., an optic disc with small diameter and small cup-to-disc ratio), optic disc drusen and optic disc edema[37] would not be known by prescribers; therefore, more obvious risk factors, such as blindness in one eye, older age, smoking, dyslipidaemia, and hypertension[37-39] should be flagged. Whilst the pathogenesis of NAION is not clear, it is generally agreed that reduced perfusion pressure in the blood vessels supplying the optic nerve leading to ischemia of the optic nerve is the primary cause;[40] therefore, significant reductions in blood pressure may contribute to NAION. When initiating or increasing GLP-1RAs, close blood pressure monitoring, along with an awareness of the potential requirement to modify background hypertension medication is recommended in those at risk of NAION. The panellists recommended that discussions regarding high-risk consequences of GLP-1RA initiation and ocular events should be held between the individual with these risk factors, their diabetologists and their ophthalmologists. This raised the importance and requirement of good co-ordination and communication across specialities.

Screening for ocular events

There was good consensus (78%) that 'when prescribing GLP-1RA therapy in people with T2DM, all should have been screened for DR within the past 12 months prior to initiation and should be monitored for any signs of ocular complications'. Interestingly there was higher consensus among diabetes and obesity specialists (82%) as compared with ophthalmologists

(71%). The panellists suggest this may reflect capacity concerns regarding ophthalmology services.

The panellists discussed that in the UK, people with T2DM are generally screened every one or two years; however, this is not the same worldwide, or for those on GLP-1RAs for weight loss only. It was agreed that any treatment intensification involving a potential rapid reduction in glucose within a short time period should be supported by retinal screening for people with diabetes. These recommendations are in line with the current UK NICE guidelines which state that when a person starts treatment that is likely to result in a rapid, substantial drop in the persons HbA1c, the person's ophthalmologist should be notified.[41] Thus, the panel recommend that people with T2DM prescribed a GLP-1RA should have a retinal screen within the previous 12 months, particularly those with a long duration (>10 years), poor glucose control (HbA1c >10%) or with established retinopathy. Additionally, people initiating GLP-1RAs for weight loss should consider checking their HbA1c status to rule out possible undiagnosed T2DM.

The panellists also agreed the importance of good communication between specialties to optimise patient care, by avoiding any delays in screening and/or prescribing, and to alleviate the observed concerns from the ophthalmologists. The panellists agreed that availability and access to ophthalmology care should not, in theory, be a barrier to optimum diabetes management. The importance of successful working relationships across disciplines, including efficient communication is known to be crucial for good patient care and must be encouraged.

Strengths and limitations

Developing consensus recommendations by a multi-disciplinary team following the ACCORD guidance for modified Delphi studies, ensures a robust methodology.[13] The Delphi questionnaire was completed by independent, voluntary (non-reimbursed) participants from across Europe. Although participants from a wide range of European nationalities completed

the questionnaire, it should be acknowledged that not all countries were represented, and no individuals outside of Europe were invited to participate, which may limit global generalizability. Final recommendations were confirmed by the expert steering committee and several of the Delphi participants, with consideration and incorporation of the comments provided from all Delphi participants. We should acknowledge that not all stakeholders were represented in the Delphi, for example, those currently taking GLP-1RAs were not included. Additionally, the Delphi questionnaire categorised GLP-1RA therapies broadly without distinguishing between different types, and did not seek consensus on individual GLP-1RA agents. Furthermore the questionnaire did not specify Glucose-dependent insulinotropic polypeptide/GLP-1 receptor co-agonists. However, as discussed above, the majority of published evidence reporting ocular risk and GLP-1RAs is related to semaglutide and tirzepatide, additionally these are the most commonly prescribed agents for weight loss;[42] thus, it was in this context we initiated the research. Therefore tirzepatide (a GLP-1/GIP agonist) was included in the search strategy and considered by panellists in their discussions. Furthermore, this study did not consider the effect of switching GLP-1RA therapy on ocular risk, these limitations are suggested areas for future investigation.

In conclusion, this Delphi study has consolidated opinions from an international, multi-disciplinary group to develop consensus recommendations in relation to GLP-1RA therapy and the risk of ocular events. Confirming that the benefits of GLP-1RAs are deemed to outweigh potential ocular risks; however, when prescribing GLP-1RAs to those with sight loss in one eye or a history of NAION, caution is advised in GLP-1RA use with detailed therapeutic risk versus benefit evaluation. The consensus recommendations will aid clinical decision making to facilitate optimum management of GLP-RA therapy in people with T2DM and obesity, whilst improving safety and efficiency via appropriate screening and improved

communication. In addition, the study directs research efforts to address clinician concerns in areas of ongoing uncertainty.

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Conflict of Interest

PC, AM and CH are employees of Health Economics and Outcomes Research Ltd. Health Economics and Outcomes Research Ltd are a consultancy company who support pharmaceutical companies (including Novo Nordisk, Eli Lilly, Pfizer Inc, GlaxoSmithKline, Amgen Inc and AstraZeneca) in their market access activities; Health Economics and Outcomes Research Ltd. did not receive any funding in relation to this study.

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Author Contributors

PC and ME conceptualised and designed the study. PC, AG, CH, ME, RS, MLA and IP developed the Delphi statements. PC, AG, CH were responsible for conduct and data analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript, and approval of the final manuscript for publication. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Data Sharing and Data Accessibility

Data generated by this study are not publicly available, but are available from the corresponding author on reasonable request.

Ethics approval

We completed the Health Research Authority (HRA) and UK Medical Research Council (MRC) decision tool to determine that this research did not require ethics committee approval (https://www.hra-decisiontools.org.uk/ethics/). The NHS HRA and UK MRC have the authority to waiver such studies from ethics committee approval; the NHS HRA and UK MRC deemed ethics approval was not necessary for our study according to their legislation [see supplementary material]. All participants were made aware their participation was voluntary, and provided informed consent to participate. Participants were also made aware their responses were anonymous and they could withdraw at any time. We conducted the study according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines as appropriate.

Legends to figures

Figure 1. Overview of the modified Delphi approach

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Tables

Table 1. Consensus agreed statements on GLP-1RAs

Treatment effects	Agreement, %
There is unequivocal evidence on the blood lowering effects of GLP-1RA therapy for people with type 2 diabetes mellitus	94
There is unequivocal evidence that GLP-1RAs are effective treatments for weight loss	94
The effectiveness of blood glucose lowering in people with type 2 diabetes mellitus is influenced by the method of GLP-1RA administration	80
The risk of major cardiovascular events is reduced significantly by GLP-1RA treatment in people who have type 2 diabetes mellitus and/or obesity	96
The use of GLP-1RA therapy prevents the onset of type 2 diabetes mellitus in individuals who are pre-diabetic (defined as HbA1c levels between 42mmol/mol (6%) and 47mmol/l (6·4%))	80
Real-world evidence	
Robust, well designed real-world evidence reporting safety outcomes influences my clinical practice when prescribing GLP-1RA therapy	94
Robust, well designed real-world evidence reporting effectiveness outcomes influences my clinical practice when prescribing GLP-1RA therapy	92

GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, haemoglobin A1c;

Table 2. Consensus agreed adverse events associated with GLP-1RA therapy

Gastrointestinal events
There is strong consensus (≥75%) that GLP-1RAs have a negative effect on the following gastrointestinal conditions: • Gastroparesis • Nausea • Vomiting • Diarrhoea • Dyspepsia • Gastroesophageal reflux disease • Gastritis • Abdominal pain • Pancreatitis

GLP-1RA, glucagon-like peptide-1 receptor agonists

Table 3. Consensus statements on GLP-1RAs and ocular events

Good consensus (≥75% agreement)	Agreement, %
Retinopathy worsening events in relation to GLP-1RA therapy are mainly caused by the rapid blood glucose lowering effect of treatment	94
People with advanced stages of diabetic retinopathy are at greater risk of disease worsening/progression on GLP-1 RA therapy	94
When prescribing GLP-1 RA therapy in those with type 2 diabetes mellitus, ALL patients should have been screened for diabetic retinopathy within the past 12 months prior to initiation and should be monitored for any signs of ocular complications	78
Some consensus (60–74% agreement)	
GLP-1 RA treatments mitigate inflammatory response in the retina and protect retinal cells from degeneration	65
No consensus (<60% agreement)	
The risk of diabetic retinopathy worsening is limited to the first 12 months of treatment with GLP-1 RA	58

GLP-1RA, glucagon-like peptide-1 receptor agonists

Table 4. Multi-disciplinary consensus recommendations on GLP-1RAs and ocular events

Recommendations
Further research into the direct effects of GLP-1RA on the retina is required
Any new evidence on the association between GLP-1RA and NAION should be reported rapidly
Those at high risk of ocular events (long duration (>10 years), poor glucose control (HbA1c >10%) or with established retinopathy) should be screened for diabetic retinopathy within previous 12 months
Any treatment intensification involving a potential rapid reduction in glucose over a short time period should be supported by retinal screening
When prescribing GLP-1RA to those with sight loss in one eye and/or prior history of NAION, consideration of ocular risks is advised
Clear communication between diabetologists and ophthalmologists is essential for optimum care
Appropriate education on the natural history of early worsening of diabetic retinopathy to increase awareness across multi-disciplinary care teams is required

GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, haemoglobin A1c; NAION, non-arteritic anterior ischemic optic neuropathy.

Figures

Figure 1. Overview of the modified Delphi approach