Updated guidance on prescribing incretin-based therapy, cardiovascular risk reduction and the wider uptake of CGM

While most sensible individuals will hopefully be taking it easy and enjoying a bit of sunshine this Spring Bank Holiday, I am playing catch-up. Indeed, the latest issue of the journal, and this editorial for it, have come around very quickly and taken me a bit by surprise! There seem to be lots of competing priorities right now, and I'm sure I am not alone.

In my previous editorial, I mentioned the arrival in the UK of the first dual GIP and GLP-1 receptor agonist, tirzepatide (Mounjaro®). I imagine, by now, many clinicians will have started prescribing this agent. In this issue of the journal, Professor Steve Bain provides a timely *At a glance factsheet* summarising what tirzepatide is, its licensed indications and its position within NICE guidelines. There is a useful table summarising the reductions in HbA_{1c} observed at various doses across the SURPASS clinical trial programme, which compared tirzepatide with various other glucose-lowering agents, including insulin. Currently, only the 2.5 mg (starting dose) and 5 mg doses are available in the UK, so it is encouraging to see such favourable results for the 5 mg dose.

I don't think we will struggle to find suitable individuals for this therapy. GLP-1 RA shortages remain a problem, albeit intermittently and variably across the UK, but I have noticed individuals currently (or formerly) prescribed GLP-1 RAs becoming increasingly upset and frustrated by this in recent months. I'm sure, like me, you will have been receiving many tasks asking for advice and guidance from those unable to source their prescribed GLP-1 RA. Now that tirzepatide is available and the supply of oral semaglutide (Rybelsus®) has been restored, I have gone back to my list of individuals who have been without their incretin-based therapy, and for many there has been a significant worsening of their HbA_{1c}, along with weight gain.

Switching to tirzepatide in individuals who have taken injectable GLP-1 RA therapy before is relatively easy; however, the pen itself (a version of the KwikPen®) is a little different, and it is important for the person to understand how to prime the pen and deliver the dose correctly. Don't forget: we also need to prescribe pen needles, as these are not supplied.

New guidance from the PCDS and ABCD

The launch of tirzepatide, the discontinuation of one GLP-1 RA (Byetta®) in March 2024, and the low or intermittent supply of other GLP-1 RAs raises a lot of questions for clinicians. Therefore, the PCDS and ABCD have collaborated again to update their joint guidance on managing the GLP-1 RA shortage. This update provides a detailed pathway for tackling the various dilemmas around GLP-1 RAs that we are faced with in clinical practice. Importantly, it provides advice and tools to support clinicians in selecting suitable alternatives where there is limited or no availability.

While I suspect the number of people on twice-daily Byetta will be very small, it is worth noting, additionally, that once-daily Victoza® is out of stock until the end of 2024 and, at the time of writing, Ozempic® and Trulicity® are expected to have intermittent supply throughout 2024. The guidance recommends, if a person cannot obtain their GLP-1 RA medication for more than two weeks, to consider prescribing Rybelsus tablets or Mounjaro injections.

Updating this guidance to include advice on Mounjaro reignited discussions amongst the authors about using these drugs in people with existing retinopathy. You may recall another of our *At a glance factsheets*, also by Steve Bain, outlining the evidence regarding diabetic retinopathy in users of GLP-1 RAs, with recommendations on safe use. At the time, Mounjaro had not launched and was, therefore, not detailed in the factsheet. Thus, we have covered this in the updated PCDS/ABCD guidance.

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Citation: Diggle J (2024) Updated guidance on prescribing incretin-based therapy, cardiovascular risk reduction and the wider uptake of CGM. *Diabetes & Primary Care* **26**: 37–9

Updated guidance

Glucagon-like peptide-1 receptor agonist national shortage

Advice on selecting alternative glucose-lowering therapies when GLP-1 RAs used in the management of type 2 diabetes in adults are unavailable.

Primary Care Diabetes Society and Association of British Clinical Diabetologists

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Given that tirzepatide has not been studied in individuals with non-proliferative retinopathy requiring acute therapy, proliferative retinopathy or diabetic macular oedema, caution must be exercised in these groups. Rapid improvements in glucose have been associated with worsening of diabetic retinopathy, and therefore the following recommendations are made:

- People with an HbA_{1c} less than 86 mmol/mol (10.0%) with normal eye screening (R0M0) or background changes (R1) in the last two years can continue with the usual interval for eye screening.
  - Discuss/educate the person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.
- If significantly elevated HbA_{1c} (e.g. 86 mmol/mol [10.0%] or higher), in a person with normal eye screening (R0M0) in the last 2 years: Discuss/educate the person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.
- If significantly elevated HbA_{1c} (e.g. 86 mmol/mol [10.0%] or higher, in a person with established background retinopathy (R1): Consider discussion (or Advice & Guidance) with local diabetes team prior to initiation of treatment.
- Those with active eye disease (R2/R3 or M1) or equivalent, under specialist ophthalmology services: Discuss with their specialist team prior to initiation to allow an individualised risk/benefit approach to treatment and monitoring to be formulated.

Within the document there is a suggested pathway to follow (*Figure 1*), which I have printed as a helpful reminder when reviewing retinal screening results prior to starting Rybelsus or Mounjaro.

Sadly, macular oedema is a common complication of diabetes, but it is encouraging to learn of a trial investigating a potential new treatment for the early stages of diabetic maculopathy, which has begun at a Liverpool hospital.

Managing cardiovascular risk

We have a little while to wait for SURPASS-CVOT, the cardiovascular outcomes trial for tirzepatide, an active-comparator study versus dulaglutide 1.5 mg weekly, which is ongoing. Because the study is "event-driven", it will only report when the pre-defined number of cardiovascular endpoints have occurred. Watch this space!

Of course, cardiovascular risk reduction remains an important consideration in our management of diabetes, and we are reminded of the importance of smoking cessation in Pam Brown's *Diabetes Distilled*. An important take-home message from her summary is that quitting confers significant mortality reductions as early as 3 years after stopping, avoiding up to 5 years of life lost, while quitting for 10 years and beyond reduces mortality risk to the level of people who never smoked. Even brief interventions for smoking cessation increase quit rates and, as Pam points out, sharing the mortality benefits of quitting may be more impactful than simply warning about the hazards of smoking.

Another of our key strategies for reducing cardiovascular risk is the initiation of statins. I discussed the new NICE lipid guidelines at length in my previous editorial, but in reality I'm sure I am not alone in encountering "statin resistance" regularly. Several of my patients have cited the increase in diabetes risk that has been linked to statins as a potential cause of their diabetes and have considered stopping their statin. I would strongly recommend

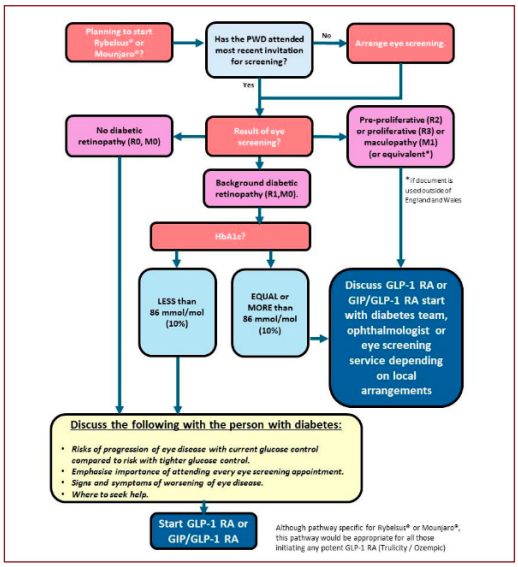

Figure 1. Suggested pathway for diabetic eye disease when starting Rybelsus or Mounjaro (Newland-Jones et al, 2024). Click to view original.

Pam's other *Diabetes Distilled* on this subject, the conclusions of which are clear: that the reduction in absolute incidence of life-threatening cardiovascular outcomes with statins in people at high risk clearly exceeds the impact of the 0.1–1.3% increased absolute incidence of type 2 diabetes per year caused by statins.

The fact that people with pre-existing diabetes treated with statins are at risk of worsening glycaemia, particularly with high-intensity statins, is another challenge. However, again, the cardiovascular benefits far outweigh this, and statin prescribing habits should not change. Rather, this is an opportunity to reinforce lifestyle discussions.

The other cornerstone of cardiovascular risk reduction is the management of hypertension, and this issue I have updated my previous guide, *How to diagnose and manage hypertension*, to reflect updated guidance from NICE (2023).

Another condition that commonly co-exists with type 2 diabetes and significantly increases the risk of cardiovascular disease is non-alcoholic fatty liver disease (NAFLD), more recently termed "metabolic dysfunction-associated steatotic liver disease (MASLD)". The mainstay of treatment for this is lifestyle changes that aim to reduce weight and waist circumference, although incretin-based therapies are currently being studied as potential therapies.

Targeting more intensive lifestyle interventions and seeking specialist advice in a timely fashion requires us to identify and monitor NAFLD/MASLD in the first place. Should we be requesting liver blood tests (AST, ALT and platelets) annually as part of our routine panel of bloods in order to be able to calculate the Fib-4 score to facilitate this? Read our *Diabetes Distilled* on the subject for the answer!

Continuous glucose monitoring

We are starting to see wider uptake of continuous glucose monitoring (CGM) in people with type 2 diabetes on insulin, and hopefully our confidence to initiate and support individuals within our practices is growing. A new e-Learning series from the PCDS is coming soon and will cover everything we need to know in primary care, from prescribing essentials to data interpretation.

Meanwhile, Samina Ali provides a short report evaluating the impact of the Freestyle Libre 2 system on diabetes distress and HbA_{1c} in people with type 2 diabetes on a twice-daily pre-mixed insulin regimen in Scotland. According to NICE (2022) NG28 recommendations, those with type 2 diabetes on multiple daily insulin injections (MDI) who fulfil additional criteria (recurrent or severe hypoglycaemia, impaired hypoglycaemia awareness, would otherwise be advised to self-monitor capillary glucose at least eight times a day, or have a condition or disability that means they cannot self-monitor capillary blood glucose) would be eligible for CGM. Similarly, in Scotland it is recommended that adults with type 2 diabetes who are on MDI should have access to CGM. However, in practice, I suspect some clinicians interpret MDI as meaning basal–bolus regimens when in fact, by definition, it means two or more injections of insulin per day. Samina's results suggest that such an interpretation may deny CGM access to a group that would certainly benefit from it.

Interestingly, with the current shortages of diabetes drugs, one of my patients recently expressed a worry that the increasing awareness of CGM technology, its wide mainstream advertising and its inclusion in commercial personalised nutrition programmes for people without diabetes could lead to sensor supply issues. I do hope not!

Having recently trialled CGM myself (although I do not have diabetes), I did not find the data gathered particularly helpful (although I was surprised to see how often physiological – and entirely asymptomatic – "hypoglycaemia" occurred, which I understand is normal!). That said, a couple of my patients diagnosed with "prediabetes" decided to self-fund CGM to gather more information about the impact of their food choices and lifestyle decisions, with much success, and I do see its utility in this group.

As I mention prediabetes, I note that within my own practice, the number of people diagnosed with non-diabetic hyperglycaemia has now overtaken the number of people on our diabetes register. It thus feels an appropriate time to go through our latest interactive case study, in which David Morris covers the clinical implications, risk factors and diagnosis of non-diabetic hyperglycaemia/prediabetes.

Until next time, I hope you find this issue helpful for your practice! ■

Read more online

How to diagnose and treat hypertension in adults with type 2 diabetes

Diagnosing and treating hypertension in accordance with updated NICE guidelines.

Diabetes & Primary Care **26**: 47–9

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References

Newland-Jones P, Beba H, Dhatariya K et al; Primary Care Diabetes Society and Association of British Clinical Endocrinologists (2024) *Update March 2024: Glucagon-Like-Peptide 1 Receptor Agonist National Shortage*. Available at: https://www.pcdsociety.org/pcds-abcd-guidance-glp1-shortage

NICE (2022) *Type 2 diabetes in adults: management* [NG28]. Available at: https://www.nice.org.uk/guidance/ng28

NICE (2023) *Hypertension in adults: diagnosis and management* [NG136]. Available at: https://www.nice.org.uk/guidance/ng136