Lipid management, tirzepatide and hybrid closed-loop: What does new NICE guidance recommend?

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I am a little late to the party but wanted to wish you all a Happy New Year. Many thanks to Nicki Milne for providing her guest editorial in the previous issue – in exchange for my chapter on insulin for her soon-to-be-published book on diabetes management in primary care (we'll let you know when it is available!).

I didn't set any New Year's resolutions this year but, nevertheless, it was disappointing to read that, in the study highlighted in Nicki's editorial, 88% of those who do, fail. Undeterred, and still feeling that levels of motivation are typically higher at the beginning of the year, I decided this might be a good time to promote the NHS Type 2 Diabetes Path to Remission Programme to the people in my care. Locally, we were fortunate to be part of the NHS England pilot programme, but uptake within my practice had not been great. I felt only partly responsible for that – 12 weeks of total meal replacement is never going to be an easy route to take – however, the desire to achieve remission of type 2 diabetes can be a compelling goal, and I didn't want anyone to miss out on the opportunity to at least consider it.

The eligibility criteria for the Path to Remission programme are presented in *Table 1*, and you can read our previous overview of the programme here. I identified 70 people who were potentially eligible for the programme (currently there are 650 people on our diabetes register). After reviewing each case, 50 people were invited to attend an afternoon information session at the practice, which included a re-cap from me on where things go wrong in type 2 diabetes and the evidence that, for some, the condition can be put into remission, as well as a presentation detailing what happens in the remission programme.

Unfortunately, the event was scheduled to take place on the one afternoon when there was a severe weather warning in place across Yorkshire – best laid plans and all that! None of the invited speakers (Xyla Health, our providers of the programme; the Regional Diabetes UK Engagement Manager; or

Table 1. Eligibility and exclusion criteria for the NHS Type 2 Diabetes Path to Remission Programme.

Eligibility criteria	Exclusion criteria
Aged 18–65 years, inclusive	Current insulin user
Diagnosed with type 2 diabetes within last 6 years	Currently breastfeeding
BMI ≥27 kg/m² (adjusted to ≥25 kg/m² in people of BAME origin)	Pregnant or planning to become pregnant within the next 6 months
Attended monitoring and diabetes review in last 12 months, including retinal screening, and commit to continue annual reviews even if remission is achieved (if newly diagnosed, no need to wait for retinal screening before making offer of referral)	Heart attack or stroke in last 6 months; severe heart failure (NYHA grade 3 or 4); severe renal impairment (most recent eGFR <30 mL/min/1.73 m²); active liver disease (not including NAFLD); active substance use disorder; active eating disorder (including binge eating); porphyria; or known proliferative retinopathy that has not been treated (not excluding individuals who are newly diagnosed and have not yet had the opportunity for retinal screening)
HbA_{1c} within 12 months, with values as follows: • If on diabetes medication, HbA_{1c} ≥43 mmol/mol (6.1%) • If not on diabetes medication, HbA_{1c} ≥48 mmol/mol (6.5%) • In all cases, HbA_{1c} must be ≤87 mmol/mol (10.1%)	Had bariatric surgery
	Health professional assessment that patient is unable to understand or meet the demands and/or monitoring requirements of the NHS Programme; or for whom the programme is not appropriate clinically (consulting with relevant Specialist teams if required); **or for whom safe and robust medications adjustment is not practical in a primary care setting**

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How to conduct an extended review for people with early-onset type 2 diabetes

A checklist of areas to cover in an extended review of type 2 diabetes in adults aged under 40 years.

Diabetes & Primary Care **26**: 15–16

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our ICB's Diabetes Project Manager) were able to make it due to the inclement weather. However, we are a hardy lot up North and all but one of the 12 patients who had accepted turned up. I gave my presentation and Xyla joined us virtually to outline the programme and answer any queries. We had an opportunity to sample a few of the meal-replacement products (not at all bad!) and I was impressed by the levels of engagement. At least half of the group have asked to be referred onto the programme, and a few more are giving it serious consideration.

Early-onset type 2 diabetes

Another of my priorities has been to seek out those with early-onset type 2 diabetes in the practice. The T2Day (Type 2 Diabetes in the Young) programme is raising awareness about this cohort of people and the serious clinical implications of type 2 diabetes occurring in the under-40s. In the previous issue of the journal, Chirag Bakhai, who is leading on the NHS England work, provided more information on the T2Day initiative.

The programme is designed to provide additional clinical support to adults under 40 with type 2 diabetes by offering an extended review to allow completion of outstanding care processes; optimisation of glycaemia, blood pressure and cardiovascular risk; weight management support; assessment of psychological needs; and, for women, discussion of contraception and pre-pregnancy planning. In this issue, Chirag has kindly returned to write a *How to* guide outlining what needs to be included in this extended review. This coincided nicely with a PCDS webinar we broadcast in early February, which is now available on demand if you missed it. To support it further, I have created a resource pack with links to topic areas of relevance – I hope you find it useful.

New NICE lipid guidelines

One element of the T2Day extended review that shocked me most was the cardiovascular risk assessment. I was aware of the pitfalls of using a 10-year risk calculator in a younger person, but I had not anticipated how much higher the calculated lifetime risk would be. In one person in my practice, in their mid-30s, the recently recorded 10-year QRISK2 score was under 10%, but when the same data was input manually into the online QRISK3 Lifetime risk calculator, her risk at 75 years was predicted to be over 30%. This, understandably, led to quite a different conversation about lipid lowering.

You may be aware that on 14 December 2023, NICE updated its guidance on *Cardiovascular disease: risk assessment and reduction, including lipid modification*, following a partial update of the guidance in May that year (NICE, 2023a). We are planning to publish a summary of the new NG238 guideline, as well as updated Q&As on lipid lowering, shortly.

The QRISK3 assessment tool is recommended in the guideline (and indeed has been for several years now); however, the tool embedded in most electronic clinical systems is still QRISK2. I suspect few clinicians will have the time or inclination to go to the QRISK3 tool online and manually enter the data required to calculate a person's cardiovascular risk. But, as I've described, the outcome for younger people can be very different. Other groups to consider using the manual QRISK3 calculator to assess cardiovascular risk are those taking corticosteroids or atypical antipsychotics, and those with systemic lupus erythematosus, migraine, severe mental illness or erectile dysfunction, because QRISK2 does not take these risk factors into account and is likely to underestimate risk.

I had anticipated that NICE would reduce its 10% risk threshold for considering lipid modification therapy in the new update, but this was not the case. However, the new advice does remind us not to rule out lipid-lowering therapy in those with a score of less than 10% if they have *"an informed preference for taking a statin or there is concern that risk may be underestimated"*.

NICE also suggests we consider offering lipid-lowering therapy without the need for a formal risk assessment to those aged 85 years or over (particularly those who smoke or have raised blood pressure), *"taking into account the risks and benefits of treatment, additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy"*.

The new guideline advocates an LDL cholesterol target of 2.0 mmol/L or less and a non-HDL cholesterol target of 2.6 mmol/L or less for people with established cardiovascular

disease. These target measures are higher than other national and international targets such as the European Society of Cardiology's (Visseren et al, 2021), because the LDL target is based on the cost-effectiveness of treatment escalation and, since the target is more affordable, it was deemed more likely to be implemented. However, this does make for some confusion!

Statins remain the first-line option but are not necessarily an easy sell. Whilst it is increasingly accepted that most side effects attributed to statins are due to a "nocebo" effect (an expectation of adverse side effects, rather than actual adverse events themselves), it is estimated that around 9% of patients are truly statin-intolerant (Bytyçi et al, 2022). In practice, I find this 2-page summary from NHS England really useful.

The NICE update refers to the increasing number of lipid-lowering therapies now available, but navigating the 48-page document isn't easy, and in practice my "go-to" remains the NHS England *Summary of national guidance for lipid management*. Work is underway to update both of these resources to match the new NICE recommendations.

Those of us who want to brush up on our knowledge of dyslipidaemia can go through David Morris' two-part interactive case study, the second part of which is in this issue. Additionally, for a summary of how some of the "newer" lipid-lowering agents work, don't forget Claire Davies' *At a glance factsheet*.

Incretin-based agents: supplies and demands

This issue, we continue our *Prescribing pearls* series with a look at the DPP-4 inhibitors, a drug class with lesser glycaemia-lowering properties than other classes but one that we may have resorted to more often over the last year given the GLP-1 receptor agonist shortages.

On the subject of GLP-1 RAs, there have been a few "developments". In last issue's editorial, Nicki signposted to the National Patient Safety Update Alert published on 3 January 2024. Supply of GLP-1 RAs continues to be limited; however, oral semaglutide (Rybelsus) is claimed to now be available in sufficient quantities to support initiation in people with type 2 diabetes, where deemed clinically appropriate.

Since then, we have had news on the first dual GIP and GLP-1 receptor agonist, more affectionately termed "twincretin". Tirzepatide (brand name Mounjaro®) landed in the UK on 12 February 2024 with assurances that there is sufficient supply to meet demand. Let's hope so, because managing the uncertainties surrounding GLP-1 RA supply has been a huge challenge for us all. Mounjaro is indicated for:

1. The treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:
   - As monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
   - In addition to other medicinal products for the treatment of diabetes.
2. Weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of:
   - ≥30 kg/m^2 (obesity), or
   - ≥27 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, type 2 diabetes).

NICE (2023b) has published Technology Appraisal guidance on *Tirzepatide for treating type 2 diabetes* on 25 October 2023 but, as yet, no guidance regarding its use for weight management. Advice on the latter is expected towards the end of May this year.

In previous issues, we provided summaries of the clinical trials for tirzepatide (SURMOUNT and SURPASS), which are worth re-visiting now the drug has launched in the UK, and we are planning an *At a glance factsheet* very soon. Already I've seen tirzepatide's arrival hitting the headlines, so we can expect an influx of enquiries. The PCDS and ABCD are also meeting to update their joint guidance on managing the GLP-1 RA shortage, and we will let you know when this is published.

Hybrid closed-loop systems

In December 2023, NICE (2023c) published its final recommendations on *Hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes*. Although the initiation and care

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Statin intolerance pathways and non-statin drugs for both primary and secondary prevention.

Diabetes & Primary Care **26**: 23

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At a glance factsheet: Hybrid closed-loop therapy

What are hybrid closed-loop systems and what do we need to know about them in primary care?

Diabetes & Primary Care **26**: 19–22

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of people using this new technology will sit with secondary care, there are still elements that primary care staff will need to know, and so I am grateful to Emma Wilmot for leading on our new *At a glance factsheet* about this subject.

At four pages in length, it is perhaps stretching our definition of "at a glance", but there was a lot to cover! It contains a host of useful information for us in primary care, including about what the devices are, what supplies will need to be on repeat prescriptions, driving regulations and managing acute illness. You can view the factsheet here.

Also in this issue

The American Diabetes Association (ADA)'s *Standards of Care in Diabetes*, as well as being "living guidelines" updated throughout the year, undergo a full update published each January. Pam Brown provides a summary of the key changes from January 2024 that are relevant to us. Meanwhile, David Morris and Probal Moulik delve into a case of new-onset diabetes in an elderly gentleman and take us through the differential diagnoses. This case turned out to be pancreatic cancer, and they outline when we should suspect this and what actions we should take.

Finally, our *Diabetes Distilled* section covers gastrointestinal events when initiating a GLP-1 RA whilst on metformin; increased cardiovascular risk associated with calcium supplementation; the optimal amount of physical activity required to improve glycaemic control in people with type 2 diabetes; and the cardiorenal benefits of achieving type 2 diabetes remission through weight loss. In addition to this journal, PCDS members can opt to receive the *Diabetes Distilled* newsletter every other month, so don't hesitate to sign up if you are not yet a member! ■

Bytyçi I, Penson PE, Mikhailidis DP et al (2022) Prevalence of statin intolerance: A meta-analysis. *Eur Heart J* **43**: 3213–23

NICE (2023a) *Cardiovascular disease: risk assessment and reduction, including lipid modification* [NG238]. Available at: https://www.nice.org.uk/guidance/ng238

NICE (2023b) *Tirzepatide for treating type 2 diabetes* [TA924]. Available at: https://www.nice.org.uk/guidance/ta924

NICE (2023c) *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes* [TA943]. Available at: https://www.nice.org.uk/guidance/ta943

Visseren FLJ, Mach F, Smulders YM et al; ESC National Cardiac Societies; ESC Scientific Document Group (2021) 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* **42**: 3227–337