Consensus Statement

Diabetes Treatments & Monitoring
Diabetes Specialist Team
MWL - STHK
2024 v13

This document was developed for internal MWL-STHK Specialist Diabetes Team use but may be of wider interest. It assumes specialist familiarity with the agents and relevant guidelines and team policies, procedures, and SOPs and the discussions which took place at Consensus Meetings in 2017-2024.

Please also consider the team's "Medications Useful Stuff" document which helps with dosing, cautions, contraindications etc. and be conscious that recommendations may change and you must consider the latest information in relevant guidelines and guidance, the BNF and SmPCs.

Introduction

The relative explosion in treatment options for the management of diabetes continues. NICE guidance continues to change and should be considered, alongside other guidance such as the Joint ADA/EASD glycemic guidelines 2015, updated 2022.

Mersey & West Lancashire Teaching Hospitals -St Helens & Whiston Hospitals (MWL-STHK) specialist diabetes team endeavours to be logical, evidence-based and consistent in its choice of diabetes treatment and recognises the need to consider value in its therapeutic choices. Confusion can arise for non-specialists if different members of the specialist team make different recommendations in ostensibly similar clinical situations, so the specialist diabetes team has always aimed to minimise seemingly *unwarranted variation* by agreeing a unified approach (consensus) to therapy & monitoring for diabetes.

The specialist team meets regularly to discuss current diabetes therapies. Considering our current understanding of the evidence-base for diabetes treatment and what is best for patients locally, we considered Type 1 and Type 2 diabetes, injectable treatments and oral agents and monitoring. This document is a summary of our discussions. It does not intend to be a comprehensive coverage of all that we do but includes some aspects of the diabetes management we deliver.

Target HbA1c

All major national and international guidelines recommend personalised targets for HbA1c in Type 1 and Type 2 diabetes.

Benefits of tight glycaemic control

Based largely on historic trials of older treatment regimens using older agents, there is compelling evidence that good glycaemic control retards the development and progression of microvascular complications, including retinopathy, nephropathy and neuropathy in Type 1 and Type 2 diabetes. The evidence for tight glycaemic control retarding the development and progression of macrovascular disease requires relatively longer-term follow-up.

The DCCT/EDIC (Type 1 diabetes) and the UKPDS (Type 2 diabetes) trials demonstrated a 'legacy effect' or 'metabolic memory': where patients exposed to a period of tight glycaemic control early in their diabetes exposure, continue to accrue benefits (relative risk reduction of microvascular and macrovascular complications) for decades after relaxation of that initial intensive control. This evidence supports an approach that achieves and where possible maintains good glycaemic control early in a patient's diabetes journey.

Thus, there is a convincing case for 'tighter' glycaemic control, especially early in a patient's diabetes exposure.

By contrast, there is also compelling evidence that glycaemic intensification in Type 1 and Type 2 diabetes increases the risk of hypoglycaemia, and in Type 2 diabetes may be associated with an increased risk of premature death, particularly in those treated with multiple drugs and in those with established vascular disease. These observations temper our approach to aggressive glycaemic control.

Balancing these conflicting priorities underpins the concept of personalised HbA1c targets.

Thus in those with Type 2 diabetes on diet alone, diet and Metformin or an alternative single OHA, where the risk of hypoglycaemia is low, we typically aim for HbA1c < 48; and as the number of drugs and the risk of or from hypoglycaemia increases (e.g. old age, frailty, reduced mobility, liver or kidney disease, dementia etc.) or where life-expectancy is reduced (and thus the risk of complication development is reduced), so the target HbA1c increases.

Target HbA1c examples in Type 2 diabetes:

- Fit & healthy, metformin treated T2DM, target HbA1c < 48
- Frail elderly, with memory problems and limited life expectancy, target HbA1c < 69
- Middle-aged man with ASCVD: target < 64
- 60-year-old on 3 OHAs, target < 58.

Target HbA1c examples in Type 1 diabetes:

- Pregnancy or pre-conception: , target < 48 (HbA1c <43 in 2nd & 3rd trimesters)
- Hybrid closed loop pump in otherwise healthy person: target < 48
- Basal-bolus regimen in otherwise healthy person: target 53 or 58
- ASCVD where risks from hypoglycemia are increased, target < 64

Insulins in Type 1 Diabetes

Rapid-acting analogues in T1DM.

Rapid-acting analogues are absorbed more quickly than soluble human insulin (injection 10-15 minutes pre-meal c.f. 20-40 minutes pre-meal respectively), which is materially more convenient for patients, so like NICE and all major guidelines, we favour rapid-acting analogue insulin over human soluble insulin in the routine outpatient management of Type 1 diabetes. There is no compelling evidence that any one rapid-acting insulin analogue is superior to any other in terms of safety or efficacy and all now have acceptable injection devices ('pens').

We do not believe current evidence supports routine use of super-fast acting analogues, such as Fiasp (slightly faster onset, but more early hypo, no material improvement in HbA1c and potential increased cost [depending on delivery device c.f. usual choices]). There may be a case for Fiasp or similar in some children and adults where food consumption is very erratic. We have therefore based our routine choice on acquisition cost.

Type 1 Diabetes - Fast-acting analogue – Insulin Trurapi (Solostar)

Long-acting analogues in T1DM.

Long-acting insulin analogues for Type 1 diabetes are also recommended in all major international guidelines because they are substantially longer-acting than NPH insulin and associated with less hypoglycaemia. Having considered duration of action, delivery device and cost, we have selected Insulin Toujeo, which is longer acting than insulin Levemir and Insulin Lantus and less expensive than Insulin Tresiba (and Lantus). It is also available as a more concentrated solution which is more convenient for patients on larger doses. N.B. our patients have historically expressed a strong preference for pre-filled pens over cartridges (c.f. cost of Abasaglar). For people with Type 1 diabetes on a basal bolus regimen, we recommend Toujeo basal insulin.

Type 1 Diabetes – Long-acting analogue – Insulin Toujeo (Solostar or Doublestar)

Insulin pump insulin in T1DM.

For insulin pumps, there is some evidence that some insulins may be associated with a higher occlusion rate and certain pumps will only accept insulin Novorapid, but the team acknowledges that Humalog is fine and there may be some instances when Fiasp is useful. The pumps we routinely offer include traditional tethered insulin pumps with tubing attached, such as Medtronic and T-slim pumps, and the patch pump, Omnipod; increasingly we offer CGM-linked, “hybrid closed loop systems” (HCL) as per NICE guidance (not discussed in detail here).

Type 1 Diabetes – Insulin pump insulin – Insulin Novorapid (Vial) or Insulin Lispro

Analog Mix in Type 1 diabetes.

A proportion of people with Type 1 diabetes choose a twice daily fixed mixture in preference to the NICE-recommended default basal-bolus regimen. There is no evidence to suggest that any one twice daily insulin analogue mix is superior to any other, so our choice is based on acquisition cost and availability of supporting patient information. We debated considering a human insulin mix but having to take the injection typically some 20-40

minutes pre-meal is materially inconvenient for patients and leads to reduced efficacy when it is taken closer to the meal. Literature for some mixes is not readily available at present.

Type 1 Diabetes – Analogue Mix – Insulin Humalog Mix 25 (Kwikpen)

Insulins in Type 2 Diabetes

Long-acting analogues in T2DM.

Some people with Type 2 diabetes are inadequately controlled despite lifestyle modification, tablets and/or other injectable agents and require insulin therapy. Sometimes, initially, this is a bedtime injection of longer-acting insulin in combination with tablets ("Combo treatment"). NICE guidance recommends NPH (human) insulin in this context but the overwhelming majority of practice in Europe and the US is to use longer-acting insulin analogues, not least because evidence in recent years shows analogues in this context are associated with significantly less mild, severe, and nocturnal hypoglycaemia, together with better HbA1c results.

For Type 2 patients who need a longer-acting insulin as part of their treatment regimen, either in combination with tablets or with a rapid-acting analogue (basal-bolus treatment or basal-plus treatment [now rarely used]), as in Type 1 diabetes we recommend Insulin Toujeo Solostar pen (100 units/ml). For those on larger doses we recommended the more concentrated solution via the Doublestar pen (300units/ml).

Type 2 Diabetes – Long-acting analogue – Insulin Toujeo (Solostar or Doublestar)

Rapid-acting analogues in T2DM.

As in T1DM, for the same reasons, our rapid-acting analogue of choice is Insulin Trurapi.

Type 2 Diabetes - Fast-acting analogue – Insulin Trurapi (Solostar)

Analog Mix in T2DM.

For people with Type 2 Diabetes who require a twice-daily mix, as in Type 1 Diabetes, we recommend Insulin Humalog Mix 25 (Kwikpen).

Type 2 Diabetes – Twice daily Mix – Insulin Humalog Mix 25 (Kwikpen)

Insulins and Oral Hypoglycaemics in Pregnancy

Insulins in Pregnancy.

In Gestational Diabetes, the rapid-acting analogue reportedly used most extensively is Humalog, so this is our fast-acting insulin of choice (we have therefore chosen Humulin I as our longer-acting (NPH) insulin in pregnancy so that patients new to insulin in this context need only familiarise themselves with a single injection device (Kwikpen).

Gestational Diabetes:

Fast-acting analogue - Insulin Humalog (Kwikpen);

Longer-acting NPH- Insulin Humulin I (Kwikpen)

Patients with pre-existing, insulin-treated diabetes (usually Type 1 diabetes) typically choose to stay on their pre-existing insulins (including pumps) and some people with Type 1 choose to switch to pump therapy, including hybrid closed loop, during pregnancy.

OHAs in Pregnancy.

Metformin is not licensed for use in pregnancy but is used extensively in many parts of the world and we use it.

Gestational diabetes and diabetes in pregnancy OHA - Metformin

Supporting Information Diabetes Management

- **Type 3c Diabetes**: also called 'exocrine diabetes' (diabetes secondary to pancreatic damage from conditions such as surgery, pancreatitis, hemochromatosis or pancreatic cancer etc.), manage as per Type 1 diabetes with heightened awareness of the risk of hypoglycaemia, both as a result of the underlying cause (if ETOH) and because of potentially blunted glucagon response in generalised pancreatic damage (consider a higher HbA1c target (default 64) and associated SMBG goals).

- **Target capillary blood glucose Levels (SMBG)**: In general diabetes, in those with a specific target HbA1c are illustrated below:

HbA1c target	Pre-breakfast	Pre-lunch	Pre-tea	Pre-bed
48	6 – 7	6 - 7	6 -7	7 - 8
53	7 – 8	7 – 8	7 – 8	8 – 9
58	8 – 9	8 – 9	8 – 9	9 – 10
64	9 – 10	8 – 9	8 – 9	9 – 10
69	9 – 10	9 – 10	9 – 10	10 – 13

- **Basal-Plus therapy**: In insulin-tablet combination therapy in Type 2 diabetes, consider adding long-acting bedtime insulin Toujeo (≥0.3 units/kg) to existing OHAs.

- **Introducing Insulin in T2DM**: If insulin-tablet combination treatment is unsuitable (e.g. if baseline HbA1c > 75) or insulin tablet combination therapy is used and fasting blood sugar levels are satisfactory, but they rise later in the day (escape), we recommend either a twice daily mix e.g. Insulin Humalog Mix 25 (consider 0.5 units/kg, split 2/3 AM and 1/3 PM), or a basal-bolus regimen (depending on patient preference), (consider 0.5 units/kg, split ½ long-acting bedtime insulin Toujeo and ½ in three equal doses of fast-acting insulin Trurapi pre-meals.

- **Supper Advice in T2DM**: There is no need to routinely eat supper (bedtime snack) in people with Type 2 diabetes who don't want it and aren't experiencing nocturnal hypoglycaemia.

- **Long-Acting insulin Administration Timing**: Rapid-acting analogues & analogue mixes are best given 10-15 min before relevant meal. Toujeo is not meal-related, and we typically recommend giving it at bedtime (see above), but timing is not critical.

- **Insulin Initiation Dosing**: Starting doses for insulin are tailored to the individual, but typical examples are:

  Type 1 diabetes: 0.5 units per Kg (split 2/3 AM and 1/3 PM if BD Mix or 50% basal and 50% split equally between the 3 pre-prandial doses if basal bolus regimen)

  <u>e.g. Newly diagnosed Type 1 Diabetes; 60 kg, Basal-Bolus regimen</u>:

Insulin Toujeo		15 units at bedtime +
Insulin Trurapi	5 + 5 + 5	pre-meals

  <u>e.g. Newly diagnosed Type 1 Diabetes; 60 kg, Twice daily mix:</u>

Humalog Mix 25	20 + 10	pre-breakfast & pre-tea respectively

  Type 2 diabetes: Insulin-tablet combination therapy ≥0.3 units/kg basal

insulin Toujeo dose (but likely to need up-titration):

e.g. Type 2 diabetes on Metformin & Gliclazide in maximum dose; 100kg, add:

Toujeo	30 units at bedtime

Type 2 diabetes: twice daily mix or basal bolus regimen ≥0.5 units/kg basal insulin dose (and likely to need up-titration):

e.g. Type 2 diabetes twice daily mix; 108kg, add:

Humalog Mix 25	36 (AM) + 18 (PM)

Subsequent doses in all of these regimens are adjusted on the basis of self-monitoring results (and/or CGM profiles), typically using targets described above and it may be appropriate on occasions to vary the starting doses based on clinical judgement (e.g. >0.3 units/kg starting dose in Type 2 diabetes).

- **SGLT2 Inhibitors and T1DM**: We do NOT advocate the use of SGLT inhibitors in Type 1 diabetes (and they are NOT licensed in this context).

Glucagon Like Peptide-1 (GLP-1) Agonist Therapy in Type 2 Diabetes

Single-Receptor GLP-1 Agonists (e.g. Semaglutide).

GLP treatment is typically used in Type 2 diabetes where glycaemic control is inadequate (higher than individualised target, typically <53 mmol/mol) on Metformin with typically two other oral hypoglycaemics in maximum tolerated dose (or where these are cautioned, contraindicated, not tolerated or deemed futile) and where BMI is raised (typically ≥35, but a lower BMI threshold is appropriate for non-Caucasians (reduce by 2.5 kg/m^2) and for those with any obesity-related co-morbidity likely to benefit from weight loss (see NICE 2022 and more recent updated NICE 2023 Tirzepatide guidance).

Single receptor GLP-1 agonists are NOT licensed for weight management except from Tier 3 or Tier 4 weight management services.

Semaglutide is more effective than Liraglutide (which will be withdrawn in 2025), has wide-reaching evidence of benefit and is arguably the default single-receptor GLP-1 agonist of choice (albeit Dulaglutide is a reasonable alternative if needed).

Except in the context of recent national guidance arising from the global shortage of single-receptor GLP-1 agonists, we do NOT typically recommend oral Semaglutide (Rybelsus) because it does not yet have convincing evidence of cardiovascular benefit (c.f. subcutaneous Semaglutide (Ozempic and Wegovy), which does).

Type 2 Diabetes – single-receptor GLP Therapy – Semaglutide (Ozempic)

In patients inadequately controlled on Metformin with or without additional OHAs or in whom Metformin is not appropriate, start Semaglutide (Ozempic) initially 0.25 mg once weekly for 4 weeks, then increased to 0.5 mg once weekly for at least a further 4 weeks, then increased to 1 mg once weekly thereafter (if necessary) i.e. Semaglutide maintenance dose is either 0.5 mg weekly or 1.0 mg weekly (we tend to use 1.0 mg weekly maintenance dose).

Where Gliclazide is combined with Semaglutide, our recommendation is to consider a lower dose of Gliclazide to reduce the risk of hypoglycaemia.

We await larger CVOT evidence with oral Semaglutide (Rybelsus).

At the time of this latest revision, there remains a global shortage of current single-receptor GLP-1 agonists and the DHSC instructed clinicians not to initiate or switch these drugs until the shortage resolved. Subsequently, national advice has been updated and it is now recommended to consider oral Semaglutide (Rybelsus) or Tirzepatide (Mounjaro)(see below) in people who might otherwise have received single-receptor, injectable GLP-1 receptor agonist therapy, or where these drugs are not available for a month or more.

Do NOT initiate or swap single-receptor, subcutaneous GLP agonists until the global shortage is resolved.

GLP-1 RAs in combination with insulin.

Having weighed the matter carefully as an MDT, recognising that guidelines are broad recommendations which must be weighed against the needs, informed preferences and circumstances of each individual patient, our expert consensus view is that in those patients treated with single-receptor GLP-1 agonists who do not achieve or maintain adequate glycaemic control, where ongoing single-receptor GLP-1 receptor agonist therapy in combination with insulin is the informed choice of the patient and is considered by the specialist to be likely to be in the patient's best interest and in those Type 2 patients already using insulin, where the addition of single-receptor GLP-1 receptor agonist therapy is the informed choice of the patient and is considered to be likely to be in the patient's best interest, we will continue to suggest consideration of such combination treatments to the patient's GP team. This is fully within the licence of these drugs but has been recommended

'amber retained' by Pan Mersey Medicines Management. In the present climate, the collective view of our team's medical and nursing leadership, endorsed by all of our consultants, is that we do not have the resources to deliver these combinations 'amber retained' at present but if it is the patient's fully informed preference and is judged likely to be in the patient's best interest, we will act in the patient's best interest and suggest the GP consider prescribing such a combination. As with all other suggestions made to GP teams by our specialists, it is the GP's prerogative to decide whether or not they choose to prescribe this or some other treatment since they ostensibly have more detailed and comprehensive knowledge of their patients and the wider context for that patient and they are ultimately responsible for the drug prescription and any associated monitoring. We respect this.

Dual-receptor (GLP-1 + GIP) agonists

In November 2023, following licensing in the US and Europe, NICE approved Tirzepatide, the first dual GLP/GIP receptor agonist for use in the treatment of Type 2 diabetes in the UK. The drug has also been approved by the MHRA for use in Obesity and Overweight but its use in Obesity is not relevant to this guidance and will not be considered further here (NICE is expected to produce guidance on Tirzepatide as a weight loss drug towards the end of 2024).

In the SURPASS trials, Tirzepatide has been shown to be significantly superior to all comparators tested, including Semaglutide.

Tirzepatide was associated with normalisation of HbA1c (HbA1c < 42 mmol/mol [5.7%]) in approximately half of patients and was associated with HbA1c results < 53 mmol/mol [7%] in 81-97%. Tirzepatide is also associated with dramatically greater weight loss than single-receptor GLP-1 agonists for diabetes, of the order of 13 kg in some of the studies. The results of the Tirzepatide CVOT are not yet available.

We will continue to promote informed decision making by our patients and some may choose alternative treatments for a variety of reasons (including at present lack of CVOT evidence of non-inferiority or superiority), but for many Tirzepatide is likely now to be the GLP-agonist of first choice.

Type 2 diabetes meeting NICE GLP criteria: TIRZEPATIDE (Mounjaro)

Please note that this therapy (and all other GLP therapies in patients not taking insulin) has been deemed GREEN by Pan Mersey Medicines Management meaning that it is recommended for initiation, titration, and monitoring in primary care.

To help primary care with this, when we write recommending consideration of Tirzepatide therapy, we typically include the following standardised paragraph:

Tirzepatide (Mounjaro)

Tirzepatide (Mounjaro) is a NICE-approved, first in class dual GLP-1/GIP agonist similar to Semaglutide (Ozempic) and Liraglutide (Victoza). Early indications are that Tirzepatide is superior to existing treatments for Type 2 diabetes and associated with substantial weight loss. Your patient meets NICE criteria for Tirzepatide treatment for Type 2 diabetes, which has been passed as GREEN by Pan Mersey APC for initiation in primary care. In the absence of contraindications, I would recommend you consider starting Tirzepatide at 2.5 mg weekly subcutaneously, up titrated in 2.5 mg steps at monthly intervals as per the BNF to a maintenance dose of 15 mg weekly. Supporting materials, including associated healthy eating advice and instructional videos can be found by searching UK websites for 'Mounjaro' (Tirzepatide) via a web browser.

2024 National Guidance re Diabetic Retinopathy and GLP therapies

Background

Some evidence suggests that diabetic retinopathy (DR) may worsen during GLP-1 agonist therapy. There is also very long-standing evidence of a typically transient deterioration in DR associated with rapid improvement in glycaemic control. It is unknown whether the deterioration in DR associated with GLP-1 agonist therapy can be attributed to a rapid improvement in glycaemic control or to some other mechanism.

In SUSTAIN 6 (Semaglutide), there were 5 cases of 'blindness' (Snellen VA 6/60 or worse) in the Semaglutide-treated patients compared with 1 in the placebo arm, all of the Semaglutide cases had previous PDR and other eye disease such as cataracts and all had received laser and/or intravitreal injection prior to the trial (3 of the 5 patients were assessed post-trial, none of whom continued to meet the criteria for diabetes-related blindness). Assessment of the results by the Federal Drug Administration (FDA) in the US, noted that the trial design was poor (non-specific outcomes, unspecified examiner, unspecified system of examination and lack of any permanent record) and that the two groups were NOT matched at baseline with the patients randomised to Semaglutide being at higher baseline risk.

As a result, our consensus statement previously included the following recommendation:

(1) 'Patients with known pre-existing DR started on Semaglutide will be referred to Ophthalmology for monitoring until the consultant ophthalmologists are satisfied there is no ongoing risk of retinopathy deterioration (agreed with Ophthalmology

CD).'

(2) 'Patients will be counselled that there is a small risk of retinopathy deterioration and those known to have had PDR plus previous laser treatment and/or intravitreal injection will be advised of a small risk of (probably reversible) diabetes-related 'blindness' and offered Liraglutide as our preferred single receptor GLP-1 agonist in this situation.'

(3) 'Retinopathy status will be sought from the GP referral (where it should be recorded) and from the patient, but we have also requested access to the regional DR screening programme database so that we can objectively verify DR status electronically in clinic (at present, it is not possible for us to establish objectively the current retinopathy status of the patient, except when this is recorded in Eye Clinic notes or in detail in the GP referral letter). SB is pursuing this.'

What has changed

- GLP-1 agonist initiation has now been declared 'green' (primary care initiation) by Pan Mersey APC so the protections built into our GLP Start pathway no longer apply.

- Tirzepatide (Mounjaro) has been licensed and approved 'green' (primary care initiation) by Pan Mersey APC.

- Oral Semaglutide (Rybelsus) and Tirzepatide (Mounjaro) have been recommended by DHSC -MSN/2024 in March 2024 (superseding previous NPSA guidance) as alternatives to Liraglutide (Victoza) or Exenatide (Byetta) or where patients are unable to obtain Semaglutide (Ozempic) or Dulaglutide (Trulicity) for 2 weeks or more.

ABCD/PCS Guidance re GLP-1 initiation and DR

HbA1c	DR Status	Recommended action
< 86	R0M0 or R1M0 in last 2 years	Educate patient re DR risks and advise report 'significant' visual changes pre-treatment and must continue usual DR screening
≥ 86	R0M0 in last 2 years	Educate patient re DR risks and advise report 'significant' visual changes pre-treatment and must continue usual DR screening
≥ 86	R1M0	Consider discussion - seeking A&G from local diabetes team prior to initiating treatment

≥ 86	≥ R2/R3 or ≥ M1, under specialist ophthalmology	Should discuss with local *specialist team prior to initiation to allow an individualised risk benefit approach to treatment and monitoring

*it does not specify whether this specialist team is ophthalmology, diabetes or both – 'depends on local arrangements'.

Issues

This leaves the MWL (St Helens) specialist diabetes team with 3 issues:

(1) Can we recommend Tirzepatide or GLP initiation to GPs when we don't know the formal, documented retinopathy status and date of screen?

(2) What is our position on Tirzepatide or GLP initiation for those GPs seeking Advice & Guidance for HbA1c ≥ 86 with R1M0?

(3) What is our position on Tirzepatide or GLP initiation in those with ≥ R2/R3 or ≥ M1, under specialist ophthalmology if we are consulted?

Recommendations by our MDT

We devise a standardised paragraph which we include in letters where we recommend initiation of GLP-1 agonists (including Rybelsus) or GLP-1/GIP agonists.

(A) We use the same standardised paragraph from (A) as our formal response to any requests for Advice & Guidance re GLP-1 agonist or GLP-1/GIP agonist initiation in patients with HbA1c ≥86 with R1M0.

(B) We use the same standardised paragraph from (A) as our formal response to any requests for Advice & Guidance re GLP-1 agonist or GLP-1/GIP agonist initiation in patients with HbA1c ≥86 with ≥R2/R3 or ≥M1.

Standardised paragraph

Retinopathy: initiation of GLP-1 agonist or GLP-1 agonist/GIP agonist treatment for Diabetes

Evidence suggests diabetic retinopathy (DR) may worsen during GLP-1 agonist therapy. There may also be a transient deterioration in DR associated with rapid improvement in glycaemic control. It is unclear whether any DR deterioration associated with GLP-1 agonist

therapy can be attributed to rapid improvement in glycaemic control or to some other mechanism.

Despite our requests, the MWL (St Helens) specialist diabetes team does not currently have access to district diabetic retinopathy screening results that are shared with GPs. We strongly recommend that you do not initiate GLP-1 agonist therapy (e.g. Liraglutide [Victoza], Semaglutide [Ozempic or Rybelsus], Exenatide [Byetta or Bydureon] or Dulaglutide [Trulicity] or GLP-1/GIP agonist therapy (e.g. Tirzepatide [Mounjaro]) unless you know the date and result of the patient's last eye screen.

The management of every patient should be individualised, but our advice would be:

HbA1c	DR Status	Recommended action
< 86	R0M0 or R1M0 in last 2 years	Educate patient re DR risks and advise report 'significant' visual changes pre-treatment and must continue usual DR screening
≥ 86	R0M0 or R1M0 in last 2 years	Educate patient re DR risks, advise they report 'significant' visual changes pre-treatment and discuss need for increased frequency screening with community eye screening programme until it is established that DR remains absent or stable
≥ 86	≥ R2/R3 or ≥ M1, under specialist ophthalmology	Caution GLP-1 agonist or GLP-1/GIP agonist therapy unless benefits felt to outweigh DR risks, in which case we would strongly recommend referral to Ophthalmology for monitoring until it is established that DR remains stable

The combination of Tirzepatide and insulin is within the licence of the drugs, but not currently recommended by NICE or Pan Mersey (NICE has not yet made any comment on this combination). See para 2, page 7 for a relevant discussion about GLP agonist therapies in combination with insulin for some individuals with Type 2 diabetes – a similar argument might be made for Tirzepatide.

We also draw attention to recent (October 2024) MHRA guidance on use of GLP-1 RAs (aimed largely that their use for weight loss) and to recent 2024 NICE retinopathy guidance, which includes discussion of the relationship between rapid HbA1c improvement (from any treatment) and potential (typically transient), retinopathy deterioration. Unfortunately, this latter element of the NICE retinopathy guidance is unhelpfully vague, probably impractical with existing ophthalmology service resources and has the potential to compromise timely patient care if every patient who might experience substantial short-term improvements in HbA1c were to have treatment delayed pending ophthalmologist assessment. Preliminary analysis from hybrid closed loop patients (where improvements in HbA1c are to be expected) suggests that very few patients experience ≥ 22mmol/mol fall in HbA1c over 3-6 months. We will continue to monitor guidance on this subject.

It is also important to note that there is growing evidence for a pleiotropic impact of GLP-1 RAs such as Semaglutide, with recent trials demonstrating improvements in heart failure (with and without reduced ejection fraction), in obstructive sleep apnoea, in kidney disease and in coronary artery disease, ostensibly independent of HbA1c and weight loss in people with and without Type 2 diabetes.

Therapy progression in Type 2 Diabetes

Rescue Treatment

If symptomatic of hyperglycaemia, particularly in hospital inpatients where expedited discharge is in the patient's best interest, consider insulin or sulfonylurea rescue treatment, then review in clinic when BG controlled.

If recently diagnosed and significant diagnostic doubt (T1 vs T2), where judged appropriate, treat as T1, check 3 x autoantibodies (Anti-GAD, IA2, & ZnT8) and C-peptide (with simultaneous laboratory glucose), and refer to clinic. C-peptide is only useful if RBG >8.0mmol/l; likely T1DM if C-pep < 200 or C-pep <600 with ≥2 autoantibodies positive. It's always a clinical judgement.

Metformin

Consistent with all major guidelines, our recommended first-line OHA is Metformin. We recommend Metformin MR because it's less likely to cause troublesome GI side effects and Metformin plain saves approximately 15p per month over MR (depending on drug chosen, plain – 95p vs 80p for 28-day supply). Not only does using plain potentially subject patients to potentially unnecessary unpleasant GI side effects (1 in 4 patients) and loss of confidence in the drug, but it also delays glycaemic optimisation if the drug has to be switched and increases healthcare resource usage (and therefore cost) at a time when OP resources in primary and secondary care are extremely stretched).

Typical starting dose is Metformin MR 500mg od with meals, titrated over several weeks as necessary to a maximum dose of Metformin MR 2g (2000mg) daily with food.

There is controversy about the maximum efficacious dose of plain Metformin which causes confusion (2g or 3g daily in divided doses), but there is no confusion over the maximum dose of the MR preparation, which in the presence of an eGFR >45 is 2g daily – another argument for starting with the MR version of Metformin.

For plain Metformin, the BNF recommends a maximum dose of 2 g per day (but does not explain why). The SPCs (Summary of Product Characteristics) from the manufacturers state 3 g daily. The Americans variably use a maximum dose of up to 2.55 g and landmark UKPDS study of Type 2 Diabetes used 2.55 g. For many patients, for many years, the maximum dose

used in the UK has been 3 g. The reduced dose appears to be driven by a question about further efficacy above 2g (Garber et al.) rather than by safety concerns.

Where we continue to use plain Metformin, we recommend a routine maximum dose of 2g (1g b.d. plain with food), but we would not rule out using up to 3g for those already taking this dose or where the clinician and the patient agree this is most appropriate for that individual.

Metformin can safely be used to an eGFR of 45; and between 30-45 it may safely be used with eGFR monitoring. Metformin should NOT be used in those with an eGFR < 30.

There is conflicting advice about dose reduction where the eGFR is between 30 and 45 – dose should certainly be reviewed, and it may be prudent to consider a reduced dose (typical maximum Metformin MR 1g total daily dose). Recent retrospective evidence suggested a better renal outcome in those with nephropathy treated with Metformin. Metformin is safe in heart failure. Metformin should be used with caution if the ALT is >3 x the ULN, particularly if this is associated with significant alcohol excess.

Type 2 Diabetes – 1st Choice OHA – Metformin MR

What happens next?

If the patient becomes severely symptomatic at any stage, consider the need for rescue therapy with Insulin or Gliclazide (see Rescue Treatment above).

If they develop ASCVD or CHF or CKD (see below) or a QRISK3 score >10% in 10 yr or risk factors for CHD aged < 40, in the absence of contraindications, offer/consider SGLT2 inhibitor treatment (Dapagliflozin).

Recent NICE guidance (NG28, February 2022) recommends SGLT2 treatment even if people achieving target glycaemia with Metformin alone. Having established metformin is tolerated, in the absence of contraindications or relevant patient factors, those with chronic heart failure (CHF) or chronic kidney disease (CKD) (eGFR< 60 and ACR >30) or established atherosclerotic cardiovascular disease (ASCVD) should be offered SGLT2 inhibitor treatment; and those at high CV risk (QRISK3 score ≥ 10% in 10 y if age > 40; or an elevated lifetime risk defined as 1 or more CV risk factors developed before age < 40, where CV risk factors=BP↑, dyslipidaemia, smoking, obesity, FH premature CVD in first degree relative) or in DKD where eGFR< 60 and ACR 3-30, SGLT2 inhibitor treatment should be considered.

Based on breadth of indications, supporting evidence and ease of use, our recommended SGLT2 inhibitor is Dapagliflozin.

Type 2 Diabetes – If SGLT2i indicated as an immediate add-on to Metformin (see above (NICE)) – Dapagliflozin 10 mg o.d.

How is this to be implemented in practice?

If ASCVD present (or high risk – see above) and predominates

…and BMI ≤ 30 and HbA1c < 75mmol/mol, in the absence of contraindications or relevant patient factors, offer Dapagliflozin 10 mg daily added to Metformin (avoid in overt peripheral arterial disease and in those with previous DKA and if eGFR < 15). If HbA1c > 75mmol/l consider simultaneously adding Gliclazide.

…and BMI ≥ 30 and HbA1c < 75mmol/mol, discuss with the patient the relative merits of Dapagliflozin versus Semaglutide (for example, in CVOTs impact on stroke was more favourable with GLP than with SGLT2). If HbA1c > 75mmol/l simultaneously add Gliclazide. If initial HbA1c < 75 initially and HbA1c ≥53mmol/mol after 3-6 months of dual combination therapy, add and titrate Gliclazide.

If HbA1c ≥53mmol/mol after 3-6 months of Metformin + Gliclazide + Semaglutide (until ASCVD evidence for Tirzepatide from CVOT):

- and Wt loss ≥3%, stop Gliclazide & consider adding Toujeo at bedtime (see discussion above about GLP + insulin). If HbA1c has not improved materially and Wt loss <3%, consider stopping GLP Rx and add Toujeo at bedtime.

If HbA1c ≥53mmol/mol after 3-6 months of Metformin + Gliclazide + Dapagliflozin: stop Gliclazide and substitute Toujeo at bedtime or B.D. Humalog Mix 25 (dictated by patient preference, SBGM pattern and HbA1c value).
Note at present combining Tirzepatide with insulin is licensed but prohibited by Pan Mersey Medicines Management and Insulin combined with other GLP agonists is recommended amber retained by Pan Mersey, but not within the resource capabilities of our department (see discussion above).

If CHF present and predominates

And HbA1c < 75 mmol/mol, (especially if LVEF < 45%), typically add Dapagliflozin 10 mg once daily. If HbA1c > 75 mmol/mol, consider simultaneously adding Gliclazide. Dapagliflozin is less efficacious and associated with more side effects if eGFR < 45 (albeit it can be used down to eGFR 15).

If HbA1c ≥53mmol/mol after 3-6 months of Metformin + Gliclazide + Dapagliflozin: stop GLICLAZIDE and substitute Toujeo at bedtime or B.D. Humalog Mix 25 (dictated by patient preference, SBGM pattern and HbA1c value). Dapagliflozin is less efficacious and associated with more side effects if eGFR < 45 (albeit it can be used down to eGFR 15). Insulin-tablet combination therapy is rarely effective if staring HbA1c is >75.

<u>If CKD (eGFR < 60 plus ACR > 30) present and predominates</u>

- And HbA1c < 75 mmol/mol, and eGFR >25), typically add Dapagliflozin 10 mg once daily (note Metformin must be stopped if eGFR < 30). If HbA1c > 75 mmol/mol, consider simultaneously adding Gliclazide. If same but ACR 3-30, consider Dapagliflozin add-on.

- If HbA1c ≥53mmol/mol after 3-6 months of Metformin + Gliclazide + Dapagliflozin: stop Gliclazide and substitute Toujeo at bedtime or B.D. Humalog Mix 25 (dictated by patient preference, SBGM pattern and HbA1c value).

- Note: Dapagliflozin can be used down to an eGFR of 15 but is only recommended for its CKD benefits down to an eGFR of 25 (and gets less effective at lowering HbA1c at lower eGFRs).

<u>If no ASCVD, not high or moderate CV Risk, no CHF & no CKD and need for treatment escalation</u>

- Weigh the risks and benefits of all relevant treatment options with the patient and help them choose the treatment option that they consider is most suitable for them.

<u>Weighing Risks & Benefits</u>

- Cardiovascular outcomes/safety: good for SC Semaglutide, Liraglutide & Dapagliflozin. Some evidence for Metformin & Pioglitazone in lower cardiovascular risk. No evidence of benefit for Gliptins (multiple CVOT studies show no CV benefit for Gliptins) and inadequate evidence yet for Tirzepatide (awaiting CVOT completion).

- Weight: Metformin and Gliptins are neutral, Semaglutide (Ozempic) is associated with weight loss of 3-6 kg. Liraglutide (Victoza) is associated with a median weight loss of 2-3 kg; Gliclazide & Pioglitazone associated with median weight gain of 2 kg. Tirzepatide is associated with 13 kg weight loss.

- Osteoporosis: increased risk of fracture all bones, both sexes with Pioglitazone.

- Thyroid cancer: there is conflicting evidence of an increased risk of thyroid cancer with GLP treatment and this remains a controversial topic. If present, it's very rare. Do not use GLP-1 RA treatment if existing or previous thyroid cancer.

- Hypoglycaemia: increased with Gliclazide, especially in frail elderly.

- Heart failure: increased with Pioglitazone – contraindicated.

- Bladder Cancer: does not appear to be increased with Pioglitazone, but a warning remains in place. Do not use in known Ca bladder or unexplained macroscopic haematuria.

- Pancreatitis & Pancreatic Cancer: very little evidence they're increased with GLP or Gliptins. There may be a very small increase in cholangiocarcinoma with GLP-1 RAs but regulatory bodies have indicated that this is NOT a reason to withdraw these drugs. GLP-1 RAs and Gliptins may slightly increase risk of pancreatitis and may be better avoided if history of pancreatitis.

- Gallstones and gallbladder disease: increased with GLP-1 RAs and gliptins.

- Nausea, vomiting, diarrhoea, and constipation are common (about 1:10) with GLP-1 RA agonists, reduced by starting low dose and typically wears off over time. Advise to drink plenty especially if get these symptoms to avoid dehydration related problems.

- DKA: definitely increased in Type 2 (and Type 1) with SGLT2 use (sometimes with normal sugars) – warn patients. All patients started on SGLT2 inhibitor treatment should be prescribed urine ketone monitoring and advised to test for ketones if unwell irrespective of blood sugar level (see our website). Guidance on GLP-1RA use after DKA appears to be drug-specific at present.

- Distal amputations: definitely increased with some SGLT2 inhibitors. Best avoid with Dapagliflozin in PAD (especially if peripheral) even though no demonstrable increase with this drug (MHRA grouped all SGLT2is together in this regard even though evidence was primarily with Canagliflozin).

Preferred Specific Agents

Metformin – MR, generic. Use in most 1st line. Avoid if eGFR < 30; caution if eGFR 30-45; caution if ALT >3x ULN and in severe ALD. GI side effects common.

Sulfonylurea – Plain Gliclazide. Use – see above. Recent evidence examining relationship between CAD and sulfonylureas suggests increased CAD with high receptor affinity SUs e.g. Glibenclamide or Glipizide, but NOT with low receptor affinity SUs such as Gliclazide.

Glitazone – Pioglitazone. Pioglitazone – use larger BMIs, female. Avoid in heart failure/fluid retention, known or likely osteoporosis or osteopenia.

SGLT2i – Dapagliflozin. Avoid in PAD, low output states, dehydration risk; increased DKA risk and recurrent or problematic UTI or thrush. Non-significant increase in stroke in a metanalysis of the trials. Current SPC allows initiation to eGFR 15.

Gliptin – Linagliptin because it is easier to use and more practical (ok in all CKD, all liver disease and only one dose: 5mg).

- We selected Gliclazide because of its relatively low acquisition cost and widespread UK use for decades, coupled with some evidence that it's shorter duration receptor binding may be beneficial. There is no superior sulfonylurea. Pioglitazone is the only thiazolidinedione licensed for use in UK. Dapagliflozin has a favourable major CVOT and CHF and renal study evidence and is easy to use.

Other Therapies in Type 1 & Type 2 Diabetes

- Type 1 diabetes – consider adding Metformin if BMI > 25
  - Consider Orlistat, Community Lifestyle Programmes (e.g. 'Healthy Living') and Bariatric Surgery if BMI > 35 (bariatric surgery is cost-effective (NICE) & under-used.
  - Aspirin should NOT be used for primary prevention of vascular disease in Type 1 or Type 2 Diabetes
  - Statins and other lipid lowering drugs should be considered as per updated NICE guidance.

Insulin Needles, Blood Glucose Meters & Strips

- We use low acquisition cost needles, lancets, and meters (individualised) as recommended (changes a lot over time).

Prof. Kevin Hardy