Diabetes Treatments & Monitoring Consensus Statement
MWL St Helens Hospital
Diabetes Specialist Team
2023 v10

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 2017-2023.

Please also consider the team's "Medications Useful Stuff" which helps with dosing, cautions, contraindications etc but be conscious that information changes and you must also consider the latest information in the BNF and SmPCs.

Introduction

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

MWL-St Helens & Whiston Hospitals specialist diabetes team has always endeavoured 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 undertaken to minimise seemingly *unwarranted variation* by agreeing a unified approach to therapy & monitoring.

The specialist team continues to meet regularly to discuss diabetes therapies. In the light of 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.

Insulins in Type 1 Diabetes

Rapid-acting analogues are absorbed more quickly than soluble human insulin (injection 10-15 minutes pre-meal c.f. 20-40 minutes pre-meal), which is materially more convenient for patients, so like NICE and all major guidelines we favour rapid-acting analogue insulin over human soluble insulin. 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 for insulin injections (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 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 and Insulin Trurapi as mealtime rapid-acting analogue.

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

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, so we have elected to stick with insulin Novorapid, but we will keep this under review.

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

A small 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 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.

In the diabetes technology clinics, we assess suitability of people with T1DM (PwT1DM) for continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion therapy (CSII,

'PUMPS') in addition to following up those already using this technology to optimise care. With the release of the NICE Hybrid Closed Loop (HCL) TA (link), many more PwT1DM are eligible for HCL. HCL systems deliver insulin automatically using a calculation based on continuous glucose measurements with real-world evidence demonstrating these systems are more effective than standard care at maintaining glucose levels within a healthy range.

Given the long wait for the release of HCL systems, some PwT1DM have opted to program their own CGM and CSII systems to create a Do-It-Yourself (DIY) closed loop (also known as open source APS). These DIY systems are not supported by regulatory bodies. As such, healthcare professionals should not recommend DIY closed loop systems and should not provide management decisions for PwT1DM based on data or programming obtained from DIY closed loop systems. Patients using DIY closed loop systems are often extremely engaged with their diabetes and committed to achieving their diabetes goals. Healthcare professionals should continue to provide support and care to these individuals, including to:

- Respect their right to make informed choices about their own care.
- Ensure individuals making informed choices to use DIY closed loop systems do so at their own risk, including documenting risks regarding use of out-of-warranty technology.
- Document discussions with the user that DIY closed loop systems are unregulated and have no published high-quality research regarding their effectiveness.
- Continue to support NHS-funded insulin pumps and CGMs if they are used for DIY closed loop systems unless deemed clinically inappropriate.
- Advise on the risks of deterioration of retinopathy with rapid improvement in HbA1c seen in those on DIY closed loops – advise to see ophthalmologist.
- Focus consultations on the need to maintain safety (ensuring supply of back-up insulin pens, ketone testing), assessment and treatment of complications, and day-to-day aspects of living with diabetes (driving, smoking, alcohol, work, etc)."

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

Insulins in Type 2 Diabetes

Some people with Type 2 diabetes are inadequately controlled on a combination of lifestyle and tablets and require insulin therapy. Often, initially, this is a bedtime injection of longer-acting insulin in combination with tablets. NICE guidance recommends NPH (human) insulin in this context but the overwhelming majority of practice in Europe and the US is to use a longer-acting insulin analogues, not least because evidence in recent years shows analogues in this context are associated with significantly less hypo, less severe hypo and less nocturnal hypo, together with better HbA1c results.

For Type 2 patients who need a longer-acting insulin as part of their treatment regimen, we recommend, as in Type 1 diabetes, we now recommend Insulin Toujeo (Solostar). For those on large doses we recommended the more concentrated solution via the Doublestar pen.

Type 2 Diabetes - Insulin-Tablet Combination Rx – Toujeo (Solostar or Doublestar)

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)

For people with Type 2 Diabetes who require basal insulin in combination with a rapid-acting analogue (basal-bolus treatment or basal-plus treatment (we rarely use basal-plus now)), we recommend Insulin Toujeo basal longer-acting insulin (taken at bedtime) and Insulin Trurapi as the mealtime rapid-acting analogue.

Type 2 Diabetes – Basal Plus or Basal Bolus – Insulin Toujeo (Solostar) + Insulin Trurapi (Solostar).

Insulin and Oral Hypoglycaemics in Pregnancy

In Gestational Diabetes, the rapid-acting analogue reportedly used most extensively is Humalog, so this is our fast-acting insulin of choice (and 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).

Patients with pre-existing, insulin-treated diabetes (usually Type 1 diabetes) typically choose to stay on their pre-existing insulins (including pumps).

Metformin is not licensed for use in pregnancy but is used extensively in many parts of the world and we use it. Glibenclamide is licensed for use in pregnancy but no longer available.

Supporting Information

- For Type 3c diabetes also called 'exocrine diabetes' (by which we mean diabetes secondary to pancreatic damage from surgery or some other condition, such as haemochromatosis or chronic pancreatitis), 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 (it may be appropriate to consider a higher HbA1c target and SMBG goals).

- In general, typical target capillary blood glucose (SMBG) levels in those with a target

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

- In insulin-tablet combination therapy in Type 2 diabetes, if fasting blood sugar levels are 5-7, but they rise later in the day (escape), we recommend a twice daily mix (Insulin Humalog Mix 25, consider 0.5 units/kg, split 2/3 AM and 1/3 PM).

- 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.

- Rapid-acting analogues & Analogue mix best given 10-15 min before relevant meal. Toujeo is not meal-related and typically given at bedtime (see above).

- Starting doses for insulin are tailored to the individual, but typically:

  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 Sanofi 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 dose (but likely to need up-titration):

  <u>e.g. Type 2 diabetes on Metformin & Glicazide in maximum dose; 100kg, add</u>:

Toujeo	30 units at bedtime

  Subsequent doses in all of these regimens are adjusted on the basis of self-monitoring results, 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).

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

GLP-1 Agonist Therapy in Type 2 Diabetes

Single-Receptor GLP-1 Agonists (e.g. Liraglutide, 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.

Liraglutide has superior efficacy to all licenced once-daily alternative GLP-1 agonists and Semaglutide is more effective than Liraglutide and arguably the default GLP-1 agonist of choice (albeit Dulaglutide is a reasonable alternative if needed).

We do NOT recommend oral Semaglutide because it does not have convincing evidence of cardiovascular benefit (c.f. subcutaneous Semaglutide, which does).

In SUSTAIN 6, 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. There is debate about whether the deterioration can be explained solely on the basis of a rapid improvement in HbA1c (as has been found in many other studies of other agents), where over time in these other circumstances there was net benefit from the treatment.

Nevertheless, 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).

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.

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.

Type 2 Diabetes – single-receptor GLP Therapy – Semaglutide (ideally with Metformin and another suitable OHA). Recommend once-daily Liraglutide if more than minimal diabetic retinopathy, especially in insulin-treated patients.

In patients inadequately controlled on Metformin with or without additional OHAs or in whom Metformin is not appropriate, start Semaglutide 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.

Where insulin or Gliclazide are combined with Semaglutide, our recommendation is to consider a lower dose of insulin/Gliclazide to reduce the risk of hypoglycaemia. Insulin therapy in future will typically be with insulin Toujeo at bedtime.

We await larger CVOT evidence with oral Semaglutide.

There is a global shortage of all current single-receptor GLP-1 agonists and the DHSC has instructed clinicians not to initiate or switch these drugs until the shortage has resolved (DHSC suggests at least until Summer 2024).

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

In those 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 is considered desirable, we will typically add basal insulin.

Type 2 Diabetes – GLP Therapy + Basal Insulin = Semaglutide (once weekly) + Toujeo (at bedtime) and Metformin ± other OHAs where appropriate.

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.

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, 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 the NICE criteria for GLP treatment: TIRZEPATIDE typically titrated to a maintenance dose of 15mg weekly and typically in association with two OHAs (e.g. Metformin + Gliclazide).

Therapy progression in Type 2 Diabetes

Rescue Treatment

If symptomatic of BG↑, particularly in hospital inpatients where expedited discharge is in the patient's best interest, consider insulin or sulfonylurea, then review in clinic when BG controlled. If recently diagnosed and diagnostic doubt (T1 vs T2), where judged appropriate treat as T1, check autoantibodies and C-peptide (with simultaneous laboratory glucose), and refer to clinic.

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 save 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 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 either as 2g od or 1g bd 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 variable 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), 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 be 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?

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

(2) 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 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 & add Toujeo at bedtime. 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).

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).

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

- 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).

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

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.

Weighing Risks & Benefits

- Cardiovascular outcomes/safety: good for SC Semaglutide, Liraglutide & Dapagliflozin. Some evidence for Metformin, Gliclazide & Pioglitazone in lower cardiovascular risk. No

evidence of benefit for Gliptins (multiple CVOT studies show no CV benefit for Gliptins) and no evidence yet for Tirzepatide.

- Weight: Metformin and Gliptins are neutral, Semaglutide is associated with weight loss of 3-6 kg. Liraglutide is associated with a median weight loss of 2-3 kg (7-8 kg in our clinic); 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 no evidence of an increased risk of thyroid cancer with GLP treatment.

- 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 analogs but regulatory bodies have indicated that this is NOT a reason to withdraw these drugs. Gliptins may be best avoided if history of pancreatitis.

- Gallstones and gallbladder disease: increased with GLP agonists and gliptins.

- Nausea: about 1 in 4-5 patients with GLP agonists, reduced by starting low dose and typically wears off over time.

- 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).

- 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.

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 in 1 in 4.

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. 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).

Kevin Hardy