

Management of Hyperglycaemia in Type 2 Diabetes

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Key Messages:

- Diabetes Education and lifestyle advice are fundamental to patient management, as is overall consideration to the patient's risk of microvascular and macrovascular complications (e.g. glycaemic control, blood pressure management, smoking status, and cholesterol). Refer the individual to Swindon guidelines on [weight management in type 2 diabetes](#), [Swindon Physical Activity guidance](#), [Management of Lipids in Primary Care](#) and Blood pressure management as these interventions are of most value. Available at <http://www.swindondiabetes.co.uk/guidance/swindon-diabetes-guidelines>
- A structured education programme for adults with type 2 diabetes is an integral part of diabetes care and should be offered to all patients and family members/carers. (For further details of local programmes- see page 4).
- An individualised approach to diabetes care should be tailored to the needs and circumstances of the adult with type 2 diabetes in association with the patient (considerations include life expectancy, risks from polypharmacy, comorbidities etc). An adult with type 2 diabetes should be involved in the discussion about target setting.
- NICE recommends that if 2 drugs in the same class are appropriate, to choose the option with the lowest acquisition cost.
- Metformin therapy is suitable for most adults with type 2 diabetes; its use is contraindicated or not tolerated in approximately 15% of individuals (NICE NG28). Metformin is the most cost effective of the initial therapy treatments.
- There is still little evidence, for some adults, to guide management strategies on treatment combinations that do not include metformin (NICE NG28).
- Evidence for combination treatments beyond second intensification is limited (when 2 or more non-insulin based treatment combinations fail to adequately control blood glucose levels).
- There is limited evidence in relation to the long-term effects of blood glucose lowering therapies, particularly newer agents in terms of efficacy and adverse events (for example, cardiovascular outcomes).
- A HbA1c reduction of 5mmol/mol (0.5%) is considered clinically important. At each review re-assess the person's needs and circumstances and think about stopping any medicines that are not effective at 6 months.
- Refer difficult to manage patients into the Swindon Community Diabetes Service (SCDS). Referral criteria are on <http://www.swindondiabetes.co.uk/guidance/health-care-professionals/>
- NICE limits the use of self-monitoring of blood glucose to particular circumstances. E.g. oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or the person is pregnant, or is planning to become pregnant. Refer to Swindon Self-Monitoring of Blood Glucose in Diabetes Guideline (December 2016). <http://www.swindondiabetes.co.uk/guidance/swindon-diabetes-guidelines/> or Appendix 5 for a summary
- Do not offer antiplatelet therapy for adults with type 2 diabetes mellitus without cardiovascular disease.
- Driving advice: this should be an individualised decision by the clinician, using the DVLA guidance (June, 2017) (<https://www.gov.uk/government/publications/at-a-glance>)
- Consider and encourage insulin at an appropriate stage in pathway rather than continue to prescribe ineffective oral antidiabetics at significant cost

A Multifactorial Approach – Where HbA1c Management Fits In;

Diabetes is a complex condition which requires regular monitoring. RightCare recommend that patients with diabetes should receive the following nine key tests/processes done at least once a year:

- Weight (aim: healthy weight between BMI 18.5 – 24.9kg/m²). Overweight patients should aim for a 5-10% target loss.
- Blood pressure (aim: <140/80mmHg, with evidence of kidney, eye or CV damage: <130/80mmHg)
- Smoking status
- HbA1c (tailored to individual needs)
- Urinary albumin (Aim: <2.5mg/mmol for men, <3.5mg/mmol for women)
- eGFR (may have implications for medications)
- Cholesterol (total Cholesterol < 5mmol/L)
- Eye examination
- Foot examination (Risk scored as low, moderate and high)

NB. Increasing physical activity, optimising weight and diet can reduce HbA1c by 11-22 mmol/mol (1-2%) **without** the need for additional prescribing

The relative benefit of different treatments

The primary goals of T2DM management are to;

- a) improve glycaemic control to prevent microvascular complications (retinopathy, nephropathy and neuropathy)
- b) normalise CVD risk factors to reduce CV events and CV mortality.

Therefore, lifestyle advice, blood pressure monitoring and control of cholesterol level are essential components in the management of type 2 diabetes. In patients with established diabetes complications /older patients with short life-expectancy /difficult to engage to self-manage their diabetes it is advisable to concentrate on management of CV risk factors such as management of blood pressure and cholesterol.

Evidence shows that tight glycemic control may be less effective in reducing cardiovascular disease when compared to blood pressure or cholesterol lowering, as demonstrated in the chart below. It shows for every 1000 people (similar to those recruited to major trials) treated with more intensive blood glucose control (HbA1c reduction of 0.9 percentage points) only about 8 would avoid a cardiovascular event, compared with 23 in every 1000 whose cholesterol is reduced by 1mmol/L and about 29 in every 1000 whose blood pressure is reduced by 10/5mmHg.

Intervention	Number of cardiovascular events prevented for every 1000 people treated over 5 years
Lowering blood sugar by 0.9%	8
Lowering cholesterol by 1mmol/L	23
Reducing BP by 10/5	29

Relationship of reductions in cholesterol, blood pressure and HbA1c with improvements in CHD and CV outcomes ; Yudkin JS, et al. Diabetologia 2010;53:2079–85, MeReC Bulletin Vol. 21, No. 5, June 2011.

Young adults (18-25 year olds)

It should be noted that young adults who develop type 2 diabetes have significantly elevated mortality, up to six times higher than age matched controls and double that of age matched peers with type 1 diabetes. Anyone with diabetes, whether type 1 or type 2, under 25 years should be referred into the young adult GWH diabetes clinic.

Lifestyle Advice & How to Access Patient Diabetes Education

DESMOND - Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (The current service provider is Swindon Community Diabetes Service, GWH)

People diagnosed with type 2 diabetes within one year should be referred to **DESMOND Newly Diagnosed** Module (ideally within 3 months)

People who have had diabetes for more than 1 year to be referred to **DESMOND Foundation** Module (for those with established diabetes)

The aims of the DESMOND programme for patients with Type 2 Diabetes are:

- To initiate and sustain successful self-management
- To encourage self-confidence to make choices that are right for them about looking after their diabetes
- To improve their understanding of the seriousness of their diabetes

Course content includes: Food choices and exercise, understanding risk factors and diabetic complications and understanding monitoring and medication. The patient will be involved in their own individualised care planning.

Self-referral by calling: 01793 696622 OR GP/practice nurse can complete a referral form from <http://www.swindondiabetes.co.uk/guidance/health-care-professionals/referrals>. The course can be completed in one day or two half days and is offered in various locations.

Living well with Type 2 Diabetes, LIFT Psychology Service. This group course of four sessions (One session per week) teaches the patient to understand thoughts, feelings and behaviours—this will help to think about things differently and do things differently. Available via Self-referral by calling 01793 836836 or visit <https://lift-swindon.awp.nhs.uk/>

Type 2 Diabetes and Me, Diabetes UK. Free online training course. A free e-learning programme consisting of five modules designed to help understand and manage diabetes successfully. Your patients can complete it at their own pace and don't have to do it all in one go. They will learn about diet, treatment, complications and where to get support. www.type2diabetesandme.co.uk Please note this is not endorsed by NICE but may be helpful for patients unable to attend DESMOND

Patient information on “**Diabetes Education for Type 2 Diabetes in Swindon**” can also be printed from <http://www.swindondiabetes.co.uk/guidance/publications-reports-resources/>

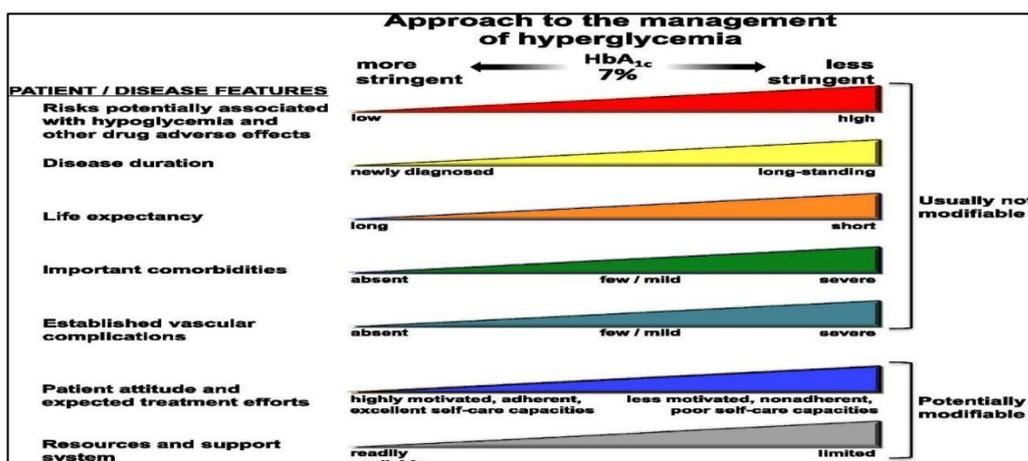
Swindon **Weight Management** and **Physical Activity** Guidelines and patient information on available resources are at <http://www.swindondiabetes.co.uk/guidance/swindon-diabetes-guidelines/> and <http://www.swindondiabetes.co.uk/guidance/publications-reports-resources/>

Personalised HbA1c Targets

The very first recommendation from NICE ([NG 28](#)) is to;

Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, any disabilities including visual impairment and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.

Involve adults with type 2 diabetes in decisions about their individual HbA1c target, the patient decision aid (appendix 3) may facilitate these discussions. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life.



This "scale" is not designed to be applied rigidly but to be used as a broad construct to help guide clinical decisions. (Adapted from Silvio E. Inzucchi et al. *Dia Care* 2015; 38:140-149).

Patient group	Guide to target HbA1c (this must be individualised)
Preconception in women	< 48mmol/mol (6.5%)
Patients managed by lifestyle and diet	< 48mmol/mol (6.5%)
If all the following apply: <ul style="list-style-type: none"> Younger patients < 60 years within 10 years of diagnosis Without established macrovascular disease (IHD, CVA, PVD) Taking a single oral agent which is not associated with risk of hypoglycaemia 	<48mmol/mol (6.5%)
If all the following apply: <ul style="list-style-type: none"> Younger patients < 60 years within 10 years of diagnosis Without established macrovascular disease (IHD, CVA, PVD) Low risk for serious consequences of hypoglycaemia Taking more than one agent Without significant comorbidities CKD or retinopathy 	<53mmol/mol (7%)
If life expectancy >10 years and any of the following apply: <ul style="list-style-type: none"> Age > 60 years or duration of diabetes > 10 years Established macrovascular disease (IHD, CVA, PVD) Tight control poses a high risk of the consequences of hypoglycaemia (e.g. risk of falling, impaired awareness of hypoglycaemia, people who drive or operate machinery as part of their job) Co-morbidities 	<58mmol/mol (7.5%)
Frail patients with reduced life expectancy (< 5 years) and / or significant co-morbidities.	Avoid levels below 58mmol/mol (7.5%). Set individual target under 85mmol/mol, taking care to avoid symptoms

Therefore, a number of factors should be taken into account when setting glycaemic targets. For instance, factors favoring setting a relatively tight glycaemic target include:

- short duration of diabetes
- long life expectancy (benefits are likely to take years to be manifest)
- absence of macrovascular complications
- low risks associated with iatrogenic hypoglycaemia
- well-motivated patient
- simple and safe treatment options available.

The glycaemic target set should regularly be reviewed and adjusted as appropriate. If serious comorbidities develop or there are difficulties with recurrent hypoglycaemia then it would be appropriate to relax the target. Remember that the "legacy effect" of good glycaemic control soon after diagnosis is still likely to result in benefits to the patient for years to come. Thus tight glycaemic control will be particularly beneficial in newly diagnosed patients.

Consider relaxing the target HbA1c level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:

- who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy
- for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, dementia, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job
- for whom intensive management would not be appropriate, for example, people with significant comorbidities

If adults with type 2 diabetes achieve an HbA1c level that is lower than their target and they are not experiencing hypoglycaemia, encourage them to maintain it.

In adults with type 2 diabetes, measure HbA1c levels at:

- 3-6 monthly intervals (tailored to individual needs) until the HbA1c is stable on unchanging therapy
- 6 monthly intervals once stable

It is imperative that lipid and blood pressure issues are addressed as these have undoubted benefits for people with diabetes. Diabetes management should come as a multifaceted package - the benefits of this approach were seen in the Steno-2 Study where substantial micro and macrovascular benefits were seen ([Gaede et al, 2008](#)) by a combined approach targeting glycaemic control, blood pressure, lipids, diet and exercise.

Never forget to reconsider the patient's diet and exercise levels as there is often scope to improve glycaemic control by addressing these issues rather than relying solely on medication.

Diabetes Type 2 Management Pathway

Patient information leaflets should be given for relevant medication. Available to print from <http://www.swindondiabetes.co.uk/guidance/publications-reports-resources>

**Suitable for primary care initiation of prescribing*

****Suitable for clinicians trained in diabetes management to initiate**

****Suitable for consultant initiation only*

- At new diagnosis
- diet and lifestyle advice, discuss weight management if BMI >25
 - prescribe DESMOND Newly Diagnosed Module
 - ***metformin standard-release**; titrate SLOWLY and trial Modified release ***SUKKARTO MR** (brand) only *if* standard release not tolerated
 - if symptomatically hyperglycaemic consider GLICLAZIDE 80mg bd 3-5 days then 160mg bd or INSULIN. Review treatment when blood glucose control achieved

Metformin contra-indicated or not tolerated

Consider SU, pioglitazone or DPP4-I, choice dependant on patient specific factors. If considering intensification, apply similar approach as if on metformin

Metformin tolerated but HbA1c >58mmol/mol

- Agree appropriate HbA1c target with NICE Patient Decision Aid (Appendix 1)
- Refer / attend DESMOND course if not done in previous 18 months
- Advice on diet, physical activity and weight loss target

REVIEW 3-6 MONTHS
(include lifestyle, lipid & BP)

IF treatment intensification appropriate, ADD one of the following in; choice dependant on patient specific factors:

BMI <25

BMI >25

***Sulphonylurea**

GLICLAZIDE standard release

Advantages:

- Rapid potent response if saved insulin reserves and no insulin resistance
- HbA1c reduction by up to 10-18 mmol/mol

Disadvantages:

- Moderate – high hypo risk
- Weight gain
- Reduce dose if eGFR < 30ml/min
- Need for self-monitoring of blood glucose (SMBG - see separate 3Ts guidance)

Cost: Low

***DPP4-I**

1st line: Alogliptin

**2nd line: Sitagliptin (HF, monotherapy),
Linagliptin (progressive CKD)**

Advantages

- Low hypo risk
- Weight neutral

Disadvantages

- Limited HbA1c lowering effect (5-10mmol/mol)
- Caution if risk of pancreatitis
- Caution if HF class III-IV – alogliptin)
- Dose adjustment required if worsening renal function (check SPCs) – except for linagliptin

Cost: High

***SGLT2-I**

**Empagliflozin
Dapagliflozin
Canagliflozin**

Any option may be beneficial in patients with established CVD

Advantages

- Low hypo risk
- Weight loss
- ↓BP
- ↓Albuminuria
- ↓ ?CV death and HF hospitalisation
- ↓ ?CKD progression
- Moderate effect on HbA1c (10-15 mmol/mol)

Disadvantages

- Not advised to initiate if eGFR < 60ml/min
- Caution in elderly (over 80)
- increased risk of genital thrush and UTIs
- Avoid with loop diuretics / volume depleted
- Risks of euglycaemic ketoacidosis
- Caution in foot ulcers (MHRA warning-canagliflozin)
- **Fournier's gangrene**

Cost: High

***Thiazolidinedione**

Pioglitazone

Advantages

- Low hypo risk
- Effective HbA1c lowering where significant features of metabolic syndrome (10-20 mmol/mol)
- Improves CV risk factors (BP, lipids)
- ↓ ? CV death, MI, fatal / non-fatal stroke

Disadvantages

- Weight gain
- Water retention
- Risks of bladder cancer, heart failure, bone fractures (avoid if present)

Cost: Low

REVIEW 3-6 MONTHS (include lifestyle, lipid & BP)

Review at 3 months to assess effectiveness

No effect/not tolerated

Try alternative dual therapy ie. STOP ineffective drug

Dual therapy effective but HbA1c > 58mmol/mol

- Refer / attend DESMOND course if not done in previous 18 months
- Advice on weight management and physical activity
- **IF** treatment intensification appropriate consider * **Triple therapy** OR ****Insulin**

Effective & tolerated → continue, review 6 monthly

Not effective (particularly if HbA1c>64mmol/mol)

Triple therapy combinations;

- Metformin, DPP4i, and SU
- Metformin, pioglitazone and SU
- Metformin, pioglitazone/SU and SGLT2i

Review after 3 months for evidence of effectiveness. Try alternative triple therapy – ie. STOP ineffective drug.

****Insulin – Refer to Swindon Insulin Guidelines for full details**

Continue metformin. Review continued need for other oral meds. Counsel re SMBG*.

Any insulins will reduce blood glucose and HbA1c. All are associated with some weight gain.

When choosing / adjusting insulin regimen, advise blood glucose testing pre meals and bedtime for 3 days prior to appointment to greatly aid safe insulin prescribing

Offer NPH insulin (**Insuman Basal, Humulin I, Insulatard**) once or twice daily

Consider starting premixed biphasic **Insuman Comb25, Humulin M3** or both NPH and short acting insulin (**** Novorapid, Humalog, Apidra**) if HbA1c is 75mmol/mol (9%) or more

Consider, as an alternative to NPH, insulin glargine (**Abasaglar**) if

- the person needs assistance to inject OR
- lifestyle is restricted by recurrent hypoglycaemic episodes OR
- would otherwise need twice daily NPH in combination with other oral drugs

PRESCRIBE ALL INSULINS BY BRAND

Longer acting analogues reduce the incidence of overnight hypo's and rapid acting analogues reduce post prandial glucose but analogues in general do not show a benefit to HbA1c over NPH insulin.

Only offer *****GLP1 with insulin** if initiated by specialist diabetes team

REVIEW 3-6 MONTHS (include lifestyle, lipid & BP)

HbA1c ≥ 86 mmol/mol

Not effective & BMI > 35 or BMI < 35 and insulin not possible due to significant occupational implications and HbA1c<86 mmol/mol. (NB. GLP1i will be ineffective if HbA1c is ≥ 86 mmol/mol. STOP last ineffective drug

****Consider GLP1**
1st line: Lixisenatide
2nd line: dulaglutide, liraglutide, exenatide prolonged release (in order of preference)
 For patients with established CVD, high CV risk, GLP1-I with proven cardiovascular benefit (currently Liraglutide) should be considered

Review continued need for other oral meds
 Require evidence of effectiveness at 6 months to continue;
 Reduction HbA1c by 1% **AND** weight loss of 3% initial weight. Ensure patient aware of this requirement; use patient contract (Appendix 2)

Advantages:	Disadvantages
Low hypo risk	GI side effects
Weight loss more likely	Risk pancreatitis
↓ Systolic BP	Injectable
↓Some CV risk factors (Liraglutide)	
Renal cautions differ within class	

Cost : High

**Suitable for primary care initiation of prescribing*

****Suitable for clinicians trained in diabetes management to initiate**

****Suitable for consultant initiation only*

Drug Summary Table

	MONTH COST (28d)	INSTRUCTIONS FOR USE	SIDE EFFECT	CAUTIONS AND CONTRAINDICATIONS	MONITORING AND STOPPING CRITERIA
Metformin Preferred MR brand = Sukkarto	Low ~£2 ~£5	Start 500mg OD (immediate release) with or after food ↑ by 500mg as tolerated (usually weekly) Usual MAX = 1000mg BD (or 850mg TDS if patient has three large starchy meals per day) although SPCs of immediate release preparations do allow for doses up to 3g/day if renal function is good. Consider trial of modified release metformin ONLY if GI tolerability prevents the person continuing with metformin despite gradual titration. Discontinue if not tolerated. Maximum dose of MR preparations is 2g/day	Gastro-intestinal side effects such as stomach discomfort, flatulence, diarrhea, nausea, metallic taste. Rarely lactic acidosis (withdraw treatment) and decreased vitamin B12 absorption. The tablet shells may be present in the faeces. Patients should be advised that this is normal.	Contraindicated in ketoacidosis, renal failure (eGFR <30 ml/min/1.73m ²), previous history of lactic acidosis, any condition predisposing to tissue hypoxia (acute cardiac or respiratory failure) If the person has mild to moderate liver dysfunction or cardiac impairment, discuss benefits of metformin so due consideration can be given to its cardiovascular-protective effects before any decision is made to reduce the dose Acute alcohol intoxication is associated with an increased risk of lactic acidosis and hypoglycemia Be aware that many other concomitant drugs may increase the chances of intolerance (see FAQ)	Determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected) Review metformin dose if eGFR <45 mL/min/1.73m ² Stop metformin if eGFR <30 mL/min/1.73m ² Iodine contrast media: Discontinue metformin at the time of or before procedure in patients with an eGFR between 30 and 60 ml/minute/1.73 m ² ; in those with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable. Elective surgery: discontinue 48 hours prior to and do not reinstate until renal function normal Advise patient to discontinue temporarily if acutely unwell and at risk for severe dehydration FBC every 3-5 years, if low Hb exclude vitamin B12 deficiency
Gliclazide	Low ~ £2	Start 40-80mg OD or BD 10-15 min before a meal, ↑ by 80mg according to response quick response (usually 3-5 days), Usual MAX = 160mg BD Try to avoid 40mg tablets if possible as they are less cost effective Introduce SMBG to assess effectiveness and then titrate dose up or down. Must carefully consider initiation and/or continued use of gliclazide in the elderly due to hypoglycaemia risks NB. will only be effective when there is some residual pancreatic beta cell activity present, without severe insulin resistance If not tolerated, other SUs may be tried (Glipizide, Glimepiride, Gliclazide MR)	Increased appetite & weight gain therefore caution if patient overweight Hypoglycaemia; provide 'Driving and Diabetes' leaflet from www.swindondiabetes.co.uk/Professionals Gastro-intestinal disturbances NB. other SUs may be considered if allergy or intolerance - see FAQs	Contraindicated in ketoacidosis Avoid concomitant use of miconazole po or oromucosal route Avoid where possible in severe hepatic impairment Use with extreme caution in frail elderly Use with caution in severe renal impairment Avoid where possible in acute porphyria Avoid during pregnancy & lactation	Frequency of hypoglycaemia Patients must have an agreed plan for SMBG

	MONTH COST (28d)	INSTRUCTIONS FOR USE	SIDE EFFECT	CAUTIONS AND CONTRAINDICATIONS	MONITORING AND STOPPING CRITERIA
Repaglinide	Low ~£5-10	Can be used as an alternative to SU on advice of specialist team only. Useful in patients with irregular meals, shift patterns, during Ramadan 0.5mg TDS immediately before or up to 30 minutes before each main meal. ↑ by 1mg according to response every 1-2 weeks MAX = 4mg TDS Introduce SMBG to assess effectiveness and then titrate dose up or down.	Gastro-intestinal side effects such as abdominal pain, diarrhoea, constipation, nausea, vomiting Hypoglycaemia (common), provide 'Driving and Diabetes' leaflet from www.swindondiabetes.co.uk/Professionals	Contraindicated in ketoacidosis Avoid where possible in severe hepatic impairment Avoid concomitant use of gemfibrozil Use with caution in renal impairment Avoid in pregnancy & lactation	Frequency of hypoglycaemia Patients must have an agreed plan for SMBG
Pioglitazone	Low ~£1	Start 15-30mg OD ↑ to 30-45mg OD according to response; higher doses are at a greater risk of side effects (include fluid retention). Elderly start at 15mg OD & ↑ gradually	Oedema increased risk of distal bone fractures in women Weight gain Upper respiratory tract infection Musculoskeletal pain Headache Erectile dysfunction Hypoesthesia Visual disturbances Anaemia	Contraindicated in ketoacidosis, cardiac failure or history of cardiac failure, hepatic impairment (including ALT > 2.5 x ULN), uninvestigated macroscopic haematuria, current or history of bladder cancer Cautioned in post-menopausal women due to increased risk of fracture Do not prescribe in a case of normal BMI and no features of insulin resistance Avoid in pregnancy & lactation	Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months Signs of oedema – exclude heart failure and consider treatment with thiazide or withdrawing treatment. MHRA risk of cardiac failure when combined with insulin Visual disturbances – be alert to possibility of macular oedema Liver function before treatment, and annually thereafter. Discontinue if ALT remains >3 x ULN
All DPP4-I 'Gliptins'	High	Use a dose appropriate to renal function Gliptins all have a limited HbA1c lowering effect so need to assess carefully for a benefit that warrants continuation.	Gastro-intestinal side effects such as constipation and nausea Peripheral oedema Upper respiratory tract infection Nasopharyngitis Musculoskeletal pain Less commonly dry mouth, anorexia, headache, drowsiness, dizziness, osteoarthritis	Contraindicated in ketoacidosis Inform patients about the symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and to tell their doctor if they have such symptoms. Discontinue if acute pancreatitis is suspected. Dose of concomitant sulfonylurea or insulin may need to be reduced to prevent hypoglycaemia Avoid in severe hepatic impairment Avoid in pregnancy & lactation	Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months Assessment of renal function is recommended prior to initiation and periodically thereafter (not linagliptin).
Alogliptin	~£26	25mg OD Reduce dose to 12.5mg if eGFR 30-49 ml/min/1.73m ² Reduce dose to 6.25mg if eGFR less than 30 mL/min/1.73m ²	See 'all DPP4-I'	See 'all DPP4-I' Avoid in Congestive heart failure NYHA III-IV	See 'all DPP4-I'
Sitagliptin	~£33	100mg OD Reduce dose to 50mg once daily if eGFR 30-49ml/min/1.73m ² reduce dose to 25 mg once daily if eGFR less than 30ml/min/1.73 m ²	See 'all DPP4-I'	See 'all DPP4-I'	See 'all DPP4-I'
Linagliptin	~£33	5mg OD	See 'all DPP4-I'	See 'all DPP4-I' Caution rather than avoid in severe hepatic impairment – limited clinical experience	See 'all DPP4-I' but no need for renal function monitoring Stop if bullous pemphigoid suspected

	MONTH COST (28d)	INSTRUCTIONS FOR USE	SIDE EFFECT	CAUTIONS AND CONTRAINDICATIONS	MONITORING AND STOPPING CRITERIA
SGLT2-I ('g iflozins')	High	<p>Avoid initiation if eGFR < 60 ml/min/1.73m²</p> <p>Advice for treating patients with SGLT2-I:</p> <ul style="list-style-type: none"> Advise increased fluid intake (at least 500 mL/day) to compensate for increased urinary fluid losses, to avoid dehydration and acute kidney injury (AKI) If HbA1c <64 mmol/mol reduce dose of SU by 50% and insulin by 20% to reduce risk of hypoglycaemia on commencing SGLT2-I. Advise patient of symptoms of genital candida infection and to commence topical clotrimazole 1% if these develop, do not stop SGLT2 	<p>Urinary Tract infection Vulvovaginal candidiasis Gastro-intestinal side effects such as constipation, nausea and thirst</p> <p>Dizziness postural, syncope</p> <p>Dyslipidaemia</p> <p>Polyuria</p> <p>Euglycaemic Ketoacidosis Fournier's gangrene</p>	<p>Do not use in patients in which type 1 DM is possible (e.g. <u>younger slim patients</u>) or in patients with a history of pancreatitis (which may lead to insulin-deficiency)</p> <p>Do not use in patients with urine ketones (> +) or in ketoacidosis</p> <p>In patients with significant symptoms of decompensated diabetes (weight loss, polyuria, polydipsia, nocturia) consider the possibility of an insulin deficient state (e.g. late onset T1DM, ketosis-prone type 2 diabetes/Flatbush diabetes/type 1.5 diabetes). Avoid SGLT2-I in such patients as may worsen risk of dehydration and, in rare cases, precipitate DKA</p> <p>Avoid in women with recurrent vulvovaginal candidiasis</p> <p>Caution in patients in whom a drop in blood pressure could pose risk</p> <p>Caution in patients with conditions that may predispose to acute kidney injury (AKI). Including hypovolaemia, CKD, CHF, concurrent diuretics, ACEi, ARB and NSAID. See FDA alert on AKI.</p> <p>Caution in patients who have risk factors for amputation (e.g. previous amputations, existing peripheral vascular disease, or neuropathy). In such patients, monitor more closely. See MHRA alert on amputations.</p> <p>Interrupt treatment in patients who: are hospitalised for major surgery (discontinue 48 hours before elective surgery due to prolonged action); have acute serious illnesses; are volume depleted (poor oral intake, diarrhoea, vomiting); have prolonged periods of fasting. Treatment may be restarted once the patient's condition has stabilised. Patients who are able to eat should substitute meals for carbohydrate rich drinks if possible (e.g. Lucozade and fruit juice).</p>	<p>Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months</p> <p>Determine renal function before treatment, 3 months after starting treatment and at least annually (due to volume depletion, small mean ↓eGFR may be observed within the first 6 weeks of treatment).</p> <p>Withhold therapy in patients who are acute volume depleted (e.g. poor oral intake, diarrhoea or vomiting) or prolonged periods of fasting, including prior to major surgery.</p> <p>If patient experiences symptoms of severe illness suggestive of DKA:</p> <ul style="list-style-type: none"> discontinue treatment with the SGLT2-I immediately if DKA is suspected or diagnosed. Check capillary blood glucose, advise increased carbohydrate intake if normal or low. refer to A&E to be screened for DKA (capillary ketones ± venous blood gas) <p>do not restart treatment with any SGLT2-I in patients who experienced DKA during use, unless another cause for DKA was identified and resolved</p> <p>Advise to carry out preventative foot care;</p> <p>If patient experiences significant lower limb complication (skin ulcer, osteomyelitis, or gangrene):</p> <ul style="list-style-type: none"> discontinue SGLT2-I at least until the condition has resolved, and continue to monitor the patient closely

	MONTH COST (28d)	INSTRUCTIONS FOR USE	SIDE EFFECT	CAUTIONS AND CONTRAINDICATIONS	MONITORING AND STOPPING CRITERIA
Empagliflozin	~£37	Do not initiate if eGFR < 60mL/min/1.73m ² Start 10mg OD If required and eGFR >60 mL/min/1.73m ² after 3 months, dose may be increased to 25mg OD If eGFR subsequently drops, 10mg OD can be continued as long as eGFR is between 45 and 60mL/min/1.73m ²	See 'All SGLT2-I'	Maximum dose of 10mg if eGFR 45-60 mL/min/1.73m ² (may be less effective and higher risk of AE). Contraindicated if eGFR <45 mL/min/1.73m ² as ineffective. Contraindicated with severe hepatic impairment (not studied) No data in pregnancy & risk during breastfeeding cannot be excluded	Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c within 6 months To be discontinued if eGFR <45mL/min/1.73m ²
Canagliflozin	~£37	Do not initiate if eGFR < 60mL/min/1.73m ² Start 100mg OD If required and eGFR >60 mL/min/1.73m ² after 3 months, dose may be increased to 300mg OD If eGFR subsequently drops, 100mg OD can be continued as long as eGFR is between 45 and 60mL/min/1.73m ²	See 'All SGLT2-I' Possible association with lower limb (primarily toe) amputation	Maximum dose of 100mg if eGFR 45-60 mL/min/1.73m ² (may be less effective and higher risk of side effects). Contraindicated if eGFR <45 mL/min/1.73m ² as ineffective. Contraindicated with severe hepatic impairment (not studied) No data in pregnancy & risk during breastfeeding cannot be excluded	Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c within 6 months To be discontinued if eGFR <45mL/min/1.73m ²
Dapagliflozin	~£37	Do not initiate if eGFR < 60mL/min/1.73m ² 10mg OD if eGFR >60 mL/min/1.73m ² If eGFR subsequently drops, 10mg OD can be continued as long as eGFR is between 45 and 60mL/min/1.73m ² Severe hepatic impairment: Start 5mg OD and increase to 10mg OD if tolerated	See 'All SGLT2-I'	Contraindicated if eGFR <45 mL/min/1.73m ² as ineffective. Caution with severe hepatic impairment (increased exposure) No data in pregnancy & risk during breastfeeding cannot be excluded Not recommended in combination with pioglitazone	Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c within 6 months To be discontinued if eGFR <45mL/min/1.73m ²
All GLP1	High	For specialist initiation only Subcutaneous injection Patient contract required at the start of treatment If HbA1c >86 mmol/mol should consider basal insulin instead. GLP1 will not be an effective treatment Advise to reduce food portion size to avoid GI side-effects	GI side effects such as nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, flatulence (may be transient) Headache Dizziness Nasopharyngitis Anorexia Bronchitis Acute pancreatitis (rare) Injection site rash	Avoid if previous pancreatitis Avoid in pregnancy & lactation May need to reduce concomitant SU or insulin dose once GLP1 initiated to reduce risk of hypoglycaemia.	Monitor treatments for anticipated benefits and stop if after 6 months HbA1c has not reduced by 11mmol/mol AND weight reduced by 3% (NICE) Be alert for GI symptoms indicative of pancreatitis and discontinue if suspected

	MONTH COST (30d)	INSTRUCTIONS FOR USE	SIDE EFFECT	CAUTIONS AND CONTRAINDICATIONS	MONITORING AND STOPPING CRITERIA
Lixisenatide	~£58	Use 1 st line 10mcg OD subcutaneous injection increasing to 20mcg after 14 days up to 1 hour before main meal (ideally similar time each day)	See All GLP1-I	Avoid if eGFR <30 mL/min/1.73m ² , use in caution if eGFR 30-60 mL/min/1.73m ²	See All GLP1-I
Dulaglutide	~£78	Consider second line if lixisenatide not tolerated or inadequate response 1.5mg ONCE WEEKLY subcutaneous injection at any time, independent of meals 0.75mg ONCE WEEKLY dose for monotherapy or as a starting dose in patients ≥ 75 years The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days (72 hours) before.	See All GLP1-I	Avoid if eGFR <15 mL/min/1.73m ²	See All GLP1-I
Liraglutide	~£78 (1.2mg) £117 (1.8mg)	0.6mg OD subcutaneous injection for 1 week, then 1.2mg OD Can increase to 1.8mg OD according to clinical response Preferably administered at the same time each day but can be independent of meals To be considered as preferable option in patients with established or at high risk of cardiovascular disease	See All GLP1-I	Avoid if eGFR < 15 mL/min/1.73m ² Avoid in severe hepatic impairment Not recommended in patients with Heart Failure NYHA IV, inflammatory bowel disease or diabetic gastroparesis Caution in thyroid goitre	See All GLP1-I
Exenatide prolonged release (Bydureon)	~£78	2mg ONCE WEEKLY subcutaneous injection ONLY if compliance issues OR district nurse administering OR excessive nausea on shorter acting lixisenatide / liraglutide	See All GLP1-I	Avoid if eGFR <50 mL/min/1.73m ² Clinical experience lacking 30-50ml/min and use is not recommended	See All GLP1-I

Renal/Hepatic Impairment – Initiating Treatment

	Renal function						Hepatic function	
	CKD stage 1 >90mL/min	CKD stage 2 60-90mL/min	CKD stage 3a 45-59mL/min	CKD stage 3b 30-44mL/min	CKD stage 4 15-29mL/min	CKD stage 5 <15mL/min	Mild/Moderate	Severe
Metformin	✓	✓	✓ (max 2g/day)	max 1g/day & review regularly (but not initiation)	✗	✗	Specialist initiation only	✗
Gliclazide	✓	✓	✓	✓	✓ (use lowest effective dose)	✗	✓	✗
Repaglinide	✓	✓	✓	✓	✓ (use lowest effective dose)	✓ (use lowest effective dose)	✓ (clinical experience is lacking)	✗
Alogliptin	25mg	25mg	12.5mg 30 – 49 mL/min		6.25mg	6.25mg	✓	✗
Sitagliptin	100mg	100mg	50mg 30 – 49 mL/min		25mg	25mg	✓	✓ lacking clinical experience
Linagliptin	✓	✓	✓	✓	✓	✓	✓	✓ lacking clinical experience
Pioglitazone	✓	✓	✓	✓	✓	✓ (monitor carefully with dialysis)	✗	✗
Empagliflozin	✓	✓	10mg od (but not initiation)	✗	✗	✗	✓	✗
Canagliflozin	✓	✓	100mg od (but not initiation)	✗	✗	✗	✓	✗
Dapagliflozin	✓	✓	10mg od (but not initiation)	✗	✗	✗	✓	✓ (start at 5mg, increase to 10mg if tolerated)
Lixisenatide	✓	✓	✓	✓	✗	✗	✓	✓
Dulaglutide	✓	✓	✓	✓	✓	✗	✓	✓
Liraglutide	✓	✓	✓	✓	✓	✗	✓	✗
Exenatide (Bydureon)	✓	✓	✗	✗	✗	✗	✓	✓
Insulin	✓	✓	✓	✓	✓ (requirement may be reduced)	✓	✓	✓ (requirement may be reduced)

Correct as of 15.2.19. For non-formulary drugs not listed here please refer to latest BNF or individual SPCs

Appendix 1 – Medication FAQs

Metformin – how is it effective and how slow to go?

Metformin treatment typically leads to a reduction in fasting plasma glucose (FPG) by 2–4 mmol/l and HbA1c by 1–2%, largely independent of age, weight and T2DM duration as long as some residual β -cell function remains.

High concentration of metformin in the upper GI tract and alteration of glucose metabolism in enterocytes lead to local irritation. More distally can cause bile salt malabsorption, which increases fluid retention in the large bowel, leading to abdominal discomfort and other gastrointestinal effects, including diarrhoea. GI side-effects can diminish if the dose is slowly titrated and reduced if necessary.

Start with 500mg od for 1 week with or after meal, increasing by 500mg each week up to 1g bd. Better tolerance is achieved with slow titration.

Around 10% of patients cannot tolerate metformin at any dose. The risk of metformin intolerance (defined as patients who stop metformin within the first 6 months of treatment) is increased by concomitant use of drugs that inhibit hOCT1 activity (including tricyclic antidepressants, citalopram, proton-pump inhibitors, verapamil, diltiazem, doxazosin, spironolactone, clopidogrel, quinine, tramadol and codeine).

Metformin & renal function - what to do?

Metformin has an oral bioavailability of 40–60% and a plasma half-life of 4–9 h, and is eliminated unchanged in the urine mostly via tubular secretion rather than glomerular filtration. Metformin does not harm the kidneys but is metabolised by the kidneys therefore need to apply some caution as the risk of lactic acidosis increases in stage IV CKD.

- Test the eGFR in any patient before you start metformin. If it's $> 45 \text{ mL/minute}/1.73 \text{ m}^2$ patient is fully eligible to be on metformin
- The FDA does not recommend **starting** metformin in patients with an eGFR between 30 and 45 $\text{mL/minute}/1.73 \text{ m}^2$.
- Still consider metformin safe if your patient is on metformin already and seems to be deriving some benefit. So, patients down to an eGFR of 30 $\text{mL/minute}/1.73 \text{ m}^2$ can remain on their metformin
- Patients with an eGFR $< 30 \text{ mL/minute}/1.73 \text{ m}^2$ should not be on metformin

How to choose the next option after Metformin

NICE recommends 4 options to consider if metformin on its own is not effective: SU, DDP-4, SGLT2 or pioglitazone. It is recommended to involve the patient into the discussion providing them with the NICE Patient Decision Aid, which may be printed from: <http://www.swindondiabetes.co.uk/guidance/publications-reports-resources:usefulresourcesfordiabetesclinics>.

You must remember these oral drugs are not miracle cures for T2D. If HbA1c >86mmol/mol, oral agents are unlikely to be effective in achieving targets; insulin should be considered in preference to other antidiabetic agents especially if the patient has symptoms of hyperglycaemia. When the patient's glucose toxicity resolves, the regimen may, potentially, be reviewed and simplified. Lifestyle changes can reduce HbA1c by 1% (the same amount as the more potent drugs).

The main points to keep in mind when considering the next anti-diabetes medication as follow:

- How long the patient has had T2DM?
- Agreed individual HbA1c target. What degree of HbA1c-lowering is required to achieve goal?
- What is current BMI? Insulin resistance vs insulin deficiency?
- Which blood glucose level is not at target: fasting or postprandial or both?
- History of cardiovascular disease
- What HbA1c reduction you can achieve prescribing selected agent (potency of the drug)?
- What adverse events are associated with selected agent(s) (hypoglycaemia, weight gain, GI, renal, CVD, heart failure outcomes)?
- What contraindications?
- What effect do selected agents have on nonglycemic parameters (weight, GI, renal, CVD, BP, heart failure)?
- What kind of life-style?
- What type of medication delivery (oral or injectable) the patients prefers?

How effective are Sulphonylureas and when to consider?

As monotherapy, sulphonylureas can lead to reductions in fasting plasma glucose by 2–4 mmol/l and HbA1c by 1–2%. Sulphonylureas can be used as first-line treatment options in patients who are intolerant of metformin, and can be used in combination with most other glucose-lowering medications, except meglitinides, which have a similar mechanism of action. The size and durability of the response to sulphonylureas is positively associated with the reserve of β -cell function and severity of insulin resistance.

To be considered in the first instance in symptomatic patients with high glucose level to achieve normoglycaemia quickly and in patients with normal weight when insulin deficiency may be suspected and a DPP4 is not tolerated or contraindicated or not effective.

Are there differences between Sulphonylureas?

Gliclazide is most commonly used but all other SUs are equally effective as potent and quick acting HbA1c lowering agents and should be considered if gliclazide has not been tolerated. Half-lives vary; gliclazide and glipizide are shorter acting whilst glibenclamide and glibenclamide have longer half-lives (over 24 hours). Gliclazide and glipizide are most suitable of all the SUs in CKD stages 3 or 4. Be wary of the longer acting SUs (including gliclazide MR) and the propensity to hypos if patients are elderly / unwell / off food for a period of time.

How to get the right dose of Gliclazide?

Gliclazide works by directly stimulating insulin secretion, so has the potential for causing hypoglycaemia. It is important to consider the time-action profile of gliclazide together with information about the patient's diet and activity, and **to introduce SBGM for a minimum 3 days prior to Gliclazide initiation.**

Onset 1-2 hours Peak 4-6 hours Half-life 8-12 hours.

If given with breakfast it will potentially lower blood glucose levels up to the evening meal.
If given with evening meal it will lower blood glucose levels pre-bed and during night.

The starting dose is usually 80 mg 15 min before a meal but consider starting with 40 mg if there are any particular concerns about hypoglycaemia. A blood glucose profile will help to identify whether to initiate a dose with breakfast or the evening meal or BD. If necessary, the dosage may be increased by 40-80 mg every 7-14 days, until a satisfactory metabolic control is achieved. The maximum dose is 320 mg/day. The usual maintenance dose is 80-160 mg in two daily administrations (before breakfast and before dinner).

An HbA1c is used as a guide to determine overall diabetes control, but is unable to indicate daily variability of BG levels or hypoglycaemia- so to titrate gliclazide it is more appropriate to use a BG profile. The BG profile and information regarding the patient's activity and diet allows an informed decision to be made as to which dose needs to be adjusted.

Remember the time-action profile of gliclazide:

If BG readings are consistently high from breakfast to the evening meal consider increasing the morning dose.

If BG readings are high after evening meal and on waking consider increasing the evening dose.

Dose Increments:

Increments of 40 – 80 mg can be made depending on how high the BG levels are:

E.g. If fasting glucose levels are only just above target (7 - 9) you can titrate up by 40 mg, however if BG levels are all in double figures 80 mg would be more appropriate.

Follow up 1 -2 weeks: To target- review again in 3 months thereafter 6 months; Not to target- Increase dose and review in 1 -2 weeks .

Hypoglycaemia with Sulphonylureas

Hypoglycaemia has been reported in 20-40% patients receiving SUs. Education and self-monitoring of blood glucose are essential in patients receiving SUs and should be initiated in everybody both before treatment starts and for ongoing maintenance. Refer to SMBG guidance for the detail [Swindon Diabetes Guidelines | Swindon Diabetes](#). Drivers will need to comply with DVLA guidance which advises testing at relevant times to driving and clinical factors.

What if SUs stop working?

The size and durability of the response to SUs is positively associated with the reserve of B-cell function, severity of insulin resistance, and diabetes duration. If HbA1c is going up on SUs consider Insulin initiation in patients with normal BMI. In overweight patients, the importance of losing weight and increase amount of physical activity needs to be highlighted, as it can result in improvement in insulin sensitivity and other options to be considered depend on the current HbA1C and a degree of HbA1c-lowering is required to achieve goal. If HbA1c is still >86 mmol/mol on dual therapy (Met+SU) consider insulin initiation as other options may reduce HbA1c by only 1%.

Where might rapid-acting secretagogues (metaglinides) be useful?

May be used instead of SUs in patients with sulfa allergies or irregular meal schedules (erratic lifestyle, shift workers, Ramadan) or in those who develop late postprandial hypoglycaemia when taking a sulfonylurea. Also may be suitable in patients with severe renal impairment. To find out the right dose of metaglinades the same approach as short-acting insulin to be used with blood glucose to be checked 6 times per day (pre-meal and 2h after) on the grounds of which every 5-7 days a decision on the need of further dose up-down titration to be made.

Pioglitazone – who does it work best in?

Can have an effective HbA1c lowering effect as the second option after metformin in obesity, and as an insulin sensitizer in overweight patients who could not tolerate both forms of metformin or metformin is contraindicated. Maximal doses can reduce HbA1c by 0.7 – 1.6% as monotherapy or combination therapy with metformin, SU or insulin. Particularly suited where there are features of metabolic syndrome, and not adequate lipid control (increased triglycerides, low HDL).

Weight gain is to be expected, 2-3kg for each 1% drop in HbA1c over the first year. The weight gain is usually in subcutaneous adipose tissue whereas visceral fat is either reduced or unaltered. Oedema (often identified by rapid weight gain) has been reported in 4-6% as the result of renal sodium reabsorption mediated by increased expression of sodium channel proteins in collecting duct epithelium.

- ✓ Obese males have the best HbA1c response without an increased side effect risk
- ✓ Females have the best HbA1c response, but are at higher risk of side effects

NB. Onset of the glucose lowering affect is gradual, taking 2-3 months to reach maximum effect.

Pioglitazone, which improves insulin sensitivity and multiple components of insulin resistance syndrome (blood pressure, lipids and endothelial dysfunction), exerts a favourable effect on CVD risk in T2D independent of its glucose-lowering action.

In PROactive study pioglitazone significantly lowered the risk of major adverse cardiovascular events (CV death, nonfatal MI and nonfatal stroke, which was the main secondary end point. Therefore, pioglitazone may be considered in patients with established CVD, but without heart failure.

When to consider a gliptin?

- ✓ Moderate control on metformin, intolerant / unsuitable for SU or pioglitazone/high hypo risk
- ✓ HbA1c <75 (higher levels would warrant Insulin or GLP1)

DPP-4 inhibitors may be an ideal choice in individuals at high risk for hypoglycaemia (i.e. elderly) or in whom a weight sparing or oral regimen is preferred.

Which gliptin?

Gliptins inhibit the enzyme which degrades the incretin hormone GLP-1. Increasing GLP-1 levels has a number of effects on glucose homeostasis by boosting glucose-dependent insulin production and inhibiting glucagon release.

DPP-4 inhibitors appear to produce more robust glycemic control the higher the starting HbA1c. In general, you may expect an HbA1c reduction by ~0.5–1% when used as monotherapy and ~0.6–1.1% when used in combination with metformin. The choice depends on balancing patient characteristics and side-effect profile rather than significant differences in glycemic efficacy.

There is a formal safety warning regarding the association of heart failure with DPP-4 inhibitors saxagliptin and alogliptin based on their assessment of the cardiovascular trials in 2016. The risk of hospitalization for heart failure remains poorly understood, and risk factors such as prior heart failure and CKD should be considered when prescribing this class of therapy.

The currently available DPP-4 inhibitors (alogliptin, sitagliptin, linagliptin, saxagliptin, vildagliptin) are licensed as monotherapy, dual therapy, triple therapy and in combination with insulin, but there are minor variations in licensing between agents.

Based on cost, Alogliptin is preferred gliptin choice locally except where;

- ✓ Cardiac failure class III or IV due to limited experience – use sitagliptin instead
- ✓ Monotherapy treatment (not licensed) – use sitagliptin instead
- ✓ *Progressive* CKD – linagliptin may be preferred as no dose adjustments required (sustained decrease in eGFR of 25% or more and a change in GFR category within 12 months or a sustained decrease in eGFR of > 15 mL/minute/1.73 m²)

Swindon CCG Community Diabetes Team support a switch programme from other gliptins to alogliptin in primary and secondary care. A switch protocol available on www.swindondiabetes.co.uk

Must check for effectiveness (HbA1c reduction > 0.5%) in 3-4 months to continue.

How SGLT2-I are effective and which SGLT2-I to use?

This class of agents inhibits the reabsorption of glucose in the proximal renal tubule and thus promotes glycosuria. This loss of glucose results in improved glycaemic control by an average 1% HbA1c reduction, loss of approximately 320 kcal/day resulting in modest weight loss and a slight fall of BP. Care should be taken if using these agents in patients with BP at target; a modest reduction in antihypertensives, especially diuretics, should be considered. Due to their mechanism of action they can be combined with most other agents though currently the combination of dapagliflozin and pioglitazone is not recommended due to concerns regarding bladder cancer.

- NICE suggests SGLT2-I's as an option along with all the other oral antidiabetic therapies – choose according to individual patient. Emerging evidence showed that all 3 agents may be beneficial in CV disease for those patients **IF** hyperglycaemia intensification is appropriate but remember to be cautious with patients at high risk of amputations (e.g. foot ulcers) in account of MHRA warning for canagliflozin.

SGLT2-Is and renal function?

SGLT2-I's work by stopping the kidneys from reabsorbing glucose. These drugs will be ineffective if renal function is reduced therefore all of SGLT2-I should only be initiated if the eGFR is >60 mL/min as they lose efficacy at lower eGFR levels. Empagliflozin and canagliflozin SPCs do allow for continuation of lower doses, dapagliflozin can continue at 10 mg if eGFR subsequently drops (as long as eGFR > 45 mL/min).

SGLT2 may also increase risk of AKI so be cautious with other drugs or conditions that may predispose patients; diuretics, ACE-I/ARB, NSAIDs, hypovolaemia, CKD, CHF.

GLP-1 RAs – how are they effective and when should they be used?

Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA) have a similar mechanism of action to the DPP-4 inhibitors but result in higher incretin levels so have additional effects on gastric emptying and satiety. They are given by subcutaneous injection. Their chief advantage is that they typically are associated with weight loss - in the range of 2-4 kg in trials, and some reduction in BP.

Their efficacy is highly variable, with trials reporting falls of HbA1c of up to 1.5% (i.e. more potent than DPP-4 inhibitors) but greater improvements are seen in selected patients.

NICE, 2015 recommends consider combination therapy (GLP-1, metformin and SU) if BMI >35 kg/m² or lower BMI when insulin is not possible due to occupational implications if triple oral therapy not effective, not tolerated or contra-indicated.

Local recommendation is for specialist or GPSI to initiate. A DESMOND course must have been attended recently by the patient before initiation and a patient contract is recommended (Appendix 3).

X - Do not use if HbA1c is > 86mmol/mol and symptoms of hyperglycaemia as treatment is unlikely to be effective enough to achieve targeted HbA1c. In such cases consider insulin initiation first or insulin dose titration.

Need to review existing oral antidiabetic therapies;

- ✓ May need to reduce a concurrent dose of SU or insulin when starting GLP-1 to reduce hypo risk
- ✓ No rationale for using GLP-1 and DPP4 together as affecting the same pathway (stop DPP4)
- ✓ Stop last ineffective drug

Review after 6 months and only continue GLP1-I where there is evidence of HbA1c reduction (11mmol/mol or 1%) **AND** weight reduction (at least 3% of initial body weight).

What are differences between GLP-1 RAs and which GLP-1 to use?

There are differences in duration of action, efficacy, tolerability, delivery device and cost.

Based on the duration of their action GLP-1 RAs are classified on short-acting (lixisenatide, exenatide) and long-acting GLP-1 RAs (liraglutide, dulaglutide, exenatide prolong-release). Short-acting GLP-1 RAs mainly reduce post-prandial glucose attributed to a reduction in gastric emptying, where are long-acting GLP-1 RAs reduce predominantly preprandial glucose with a modest effect on the reduction of gastric emptying, thus the reduction in PPG excursions can be mainly attributed to a reduction in preprandial glucose levels.

Long-acting GLP-1 appeared to be more effective in glycemic efficiency reducing HbA1c by up to 1.5-2% compared to short-acting GLP-1 RAs. Liraglutide 1.8mg daily/Dulaglutide 1.5 mg weekly according to meta-analysis are superior in glycemic control compared with others. Liraglutide 1.8mg is considered more effective in weight loss. Once-weekly preparations tend to cause less nausea.

There is also renal impairment to be considered when prescribing GLP-1 RAs (see the renal/hepatic impairment on anti-diabetic treatment initiation table above).

Based on cost, Lixisenatide is preferred choice of GLP-1 locally.

1st line lixisenatide daily

2nd line dulaglutide weekly, liraglutide daily or exenatide weekly.

Liraglutide to be considered as preferable option in patients with established or at high risk of cardiovascular disease.

Cardiovascular considerations?

The strongest evidence for cardiovascular benefit remains with metformin and this is the first-line agent of choice in the treatment of type 2 diabetes.

Insulin is safe in cardiovascular disease as long as hypoglycaemia and excessive weight gain are avoided. However, it is not mandatory and if satisfactory glycaemic control can be achieved with oral agents then insulin is not indicated.

Over rapid tightening of glycaemic control in patients with macrovascular disease should be avoided as this can be associated with cardiovascular morbidity or even mortality ([ACCORD, 2008](#)).

Pioglitazone is contraindicated in the presence of heart failure as it causes fluid retention. Metformin can be used in the presence of stable heart failure, though should be avoided at times of decompensation due to the risk of lactic acidosis.

There is now published evidence for pioglitazone, SGLT2-I (empagliflozin, canagliflozin, dapagliflozin) and GLP-1 RA (liraglutide) showing CV benefits. Therefore, these agents may be considered as the second/third option accordingly in patients with established or at high risk of cardiovascular disease (prior MI; coronary artery disease; stroke; unstable angina or occlusive peripheral arterial disease) applying initiation and stopping criteria in line with the agreed pathway.

Do I change drug / class or continue and add in another?

Keep monitoring for evidence of effectiveness. Consider with each new addition;

- Be mindful of other lifestyle interventions the patient may have implemented simultaneously (or not).
- Check concordance (or at least ordering frequency) fits with what you would expect.
- Ensure the dose of drug has been optimised.

If you are still not seeing the desired effect on HbA1c, STOP and trial an alternative.

Generally speaking, you would expect similar effects from each of the different agents within a class so if e.g. alogliptin has failed to have the desired effect, would suggest trying a different class rather than a different gliptin. The exception to this might be the GLP1s.

Again generally, if there has been intolerance to one agent, it may be worth trying an alternative from within the same class.

What about the conflict between QOF and this guidance i.e. not always treating to target?

Current QOF encourages you to treat your patients to a target HbA1c of < 53 mmol/mol. This may be at odds with NICE's recommendation to personalise HbA1c targets. We would suggest it is appropriate to treat in accordance with NICE guidance, with the necessary exception reporting in place. Documentation of discussions & decisions re targets is important, use of the NICE patient decision aid may support those discussions.

What about combination products?

Combined products are generally less preferred as there is less flexibility to tweak doses. Unless the patient has concordance problems AND the individual components are stable and already demonstrated as effective please prescribe separately. All of the DPP4-Is and SGLT-Is have combination products with metformin which can be cost effective compared to the individual ingredients options. Competact is considerably more expensive than pioglitazone and metformin given separately. Make sure you are not compromising the metformin dose by going to a combination product. See Appendix 4 for detail.

What if I have a patient on a combination of drugs NOT recommended in NICE guidance?

The Community Diabetes Team are happy to accept referrals for such patients. If a specialist is recommending combinations other than those specified in the guidance it would be reasonable to justify why.

When to consider Insulin?

A general observation; we are inappropriately postponing insulin treatment for a large cohort of patients. Many patients with type 2 diabetes eventually require and benefit from insulin therapy. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients. Providers should avoid using insulin as a threat or describing it as a sign of personal failure or punishment.

There is not much to be gained for patients continuing with multiple oral therapies and high HbA1c (>75 mmol/mol) so please consider insulin as per the pathway and refer patients to the Community Diabetes Team appropriately.

Appendix 2 – NICE Patient decision Aid for HbA1c Target

Full NICE decision aid is available at <https://www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-2187281197> or <http://www.swindondiabetes.co.uk/guidance/publications-reports-resources/>

Your target blood glucose (HbA1c) level: weighing it up

Make a mark on the lines to show how you feel about these statements. The more you agree with the statement on the left, the further to the left you should put the mark. The more you agree with the statement on the right, the further to the right you should put the mark. You and your healthcare professional can use this to help decide the best target HbA1c level for you.

Thinking about things like driving, having severe hypos would not be a problem for me*



Thinking about things like driving, having severe hypos would be a big problem for me*

I'm not bothered about the possibility of getting other side effects



Getting other side effects would be a big problem for me

I'm happy to take more medicines if I need to



I don't want to take any more medicines

I don't have any health problems apart from my diabetes



I have lots of health problems

Thinking about my age and my health overall, I'm hoping to see longer-term benefits



Thinking about my age and my health overall, shorter-term benefits are more important to me



*Hypos might also be a problem for you for other reasons, such as if you operate machinery, if you are at risk of falling, or if you find it difficult to recognise the warning symptoms of a hypo.

Appendix 3 – GLP1 Patient Contract

At your appointment today, we have agreed to start treatment with a GLP1 Agonist _____ to help manage your type 2 diabetes:

Further information on how to use the device and any side-effects you should be aware of is included in the patient information provided with your medicine supply.

Although these medicines are given as an injection, they work in a different way to insulin. However, they should help reduce your blood glucose levels and may also help you lose weight, especially if you follow a healthy diet and take regular exercise.

This anti-diabetes injection does not work for everyone and, if left unchecked, may not be the best use of NHS resources. We therefore need to regularly monitor whether it is being effective.

In order to do this, we follow the guidance from the National Institute of Health and Clinical Excellence (NICE). This states that treatment with these medicines should only be continued after 6 months if a patient sees a reduction in their HbA1c (measurement of long term blood sugar control) of 11mmol/mol (in the old number system that is about 1% HbA1c) and a reduction in their weight of 3% or more.

If the GLP-1 agonist injection we have agreed to start today does not provide these beneficial outcomes after 6 months, we will need to consider alternative options to manage your condition and stop the GLP1 agonist injection.

If treatment is continued after 6 months, we will continue to monitor your HbA1c and weight on a regular basis. If the beneficial effects are not maintained then, again, we will need to consider alternative options to manage your condition and then stop the GLP 1 agonist injection.

PATIENT AGREEMENT:

The information above has been explained to me and I understand that treatment with GLP1 Agonist will be stopped and alternative options considered if the beneficial effects on my weight and HbA1c are not achieved after 6 months, or continued long-term.

	Today	6 months' target
Weight (3% loss needed by 6 months)		
HbA1c (11mmol/mol (1%) reduction needed by 6 months)		
eGFR (to check your kidney function)		To be measured in 6 months

Patient Name: _____ Patient Signature: _____

Clinician Name: _____ Clinician Signature: _____

Date: ____/____/____ Date of 6-month review: ____/____/____

If you have any questions or problems with your treatment, please contact:

Name: _____ Contact number: _____

Please give a copy to the patient and keep a copy in the patient's record. If treatment is started by hospital clinicians, please also send a copy to the patient's GP

Appendix 4 – Self Monitoring of Blood Glucose – Recommended Frequency

Full SMBG guidance at <http://www.swindondiabetes.co.uk/guidance/swindon-diabetes-guidelines/>

NHS

Swindon
Clinical Commissioning Group

Swindon Self-Monitoring of Blood Glucose in Diabetes Guideline

Who should be offered self-monitoring of blood glucose:

Type 1 Diabetes – all patients will need to self-monitor

Type 2 diabetes - Do not *routinely* offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless:

- the person is on insulin or
- there is evidence of hypoglycaemic episodes or
- the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or
- the person is pregnant, or is planning to become pregnant (NICE 2015).

Frequency of monitoring in Type 2 Diabetes

Diet and metformin	not routinely offered	
DPP4i (gliptins), GLP-1 injectables, SGLT2 (gliflozins), pioglitazone	not routinely offered	
Sulfonylureas	maintenance – 2-3 x per week; drivers regularly	See DVLA guidance below.
	initiation, titration – twice per day (different times)	
Meglitinides	maintenance – 2-3 x per week; drivers regularly	
	initiation, titration – 4 x per day (bb, + 2 h pp)	
Basal insulin	Maximum twice daily	
Plus non SU antidiabetic	Once or twice a day	
Plus SU	Two or three times a day	
Basal insulin (twice per day)	twice daily	
Mixed insulin	2-3 x per day	
Basal bolus insulin	4 x per day	

Note - all patients should be reviewed on an individual basis taking into account specific patient factors

Special Circumstances that may require more frequent SMBG testing (frequency to be agreed with patient):

- At diagnosis for 5-7 days to understand lifestyle interventions
- Pre-post prandial level to assist in drug choice at treatment intensification
- Co-prescribed steroids
- Intercurrent illness
- Frequent hypos
- Impaired hypo awareness
- Periods of fasting
- Exercise

Appendix 5 – Annual Costs of Antidiabetic Therapies Including Combination Products

Diabetes Therapies; Treatment Options – Cost and Clinical Comparisons			
Standard Therapies			
Drug Class	Cost per patient per year		Daily doses of metformin in combination products
	Drug Alone	Combination product with metformin	
Metformin – Standard Release	£37		
Metformin – Modified Release	£110		
SU's Standard Release (Gliclazide)	£42		
SU's Modified Release (Gliclazide)	£73		
Pioglitazone	£10	£467	1.7g
Repaglinide	£120		

Newer Therapies and Insulin – Swindon CCG recommended options at top of each list				
Drug	Standard Dose	Cost per patient per year		Daily doses of metformin in combination products
		Drug Alone	Combination product with metformin	
DPP-4 Inhibitors – The Gliptins				
Alogliptin ▼	25mg daily	£347	£347	2g
Sitagliptin	100mg daily	£434	£434	2g
Linagliptin	5mg daily	£434	£434	1.7 or 2g
SGLT2 Inhibitors – The Flozins				
Empagliflozin ▼	10mg daily	£477	£477	1.7 or 2g
Canagliflozin ▼	100mg daily	£477	£477	1.7 or 2g
Dapagliflozin ▼	10mg daily	£477	£477	1.7 or 2g
GLP-1s				
Lixisenatide ▼	20mcg daily	£696		
Dulaglutide ▼	1.5mg weekly	£949		
Liraglutide	1.2mg – 1.8mg daily	£936 - £1404		
Exenatide PR	2mg weekly	£949		
Insulin – Intermediate/long acting: Costs expressed per units per day dosing				
NPH Insulin	20 units daily	£96		

Drug Tariff Jan 18